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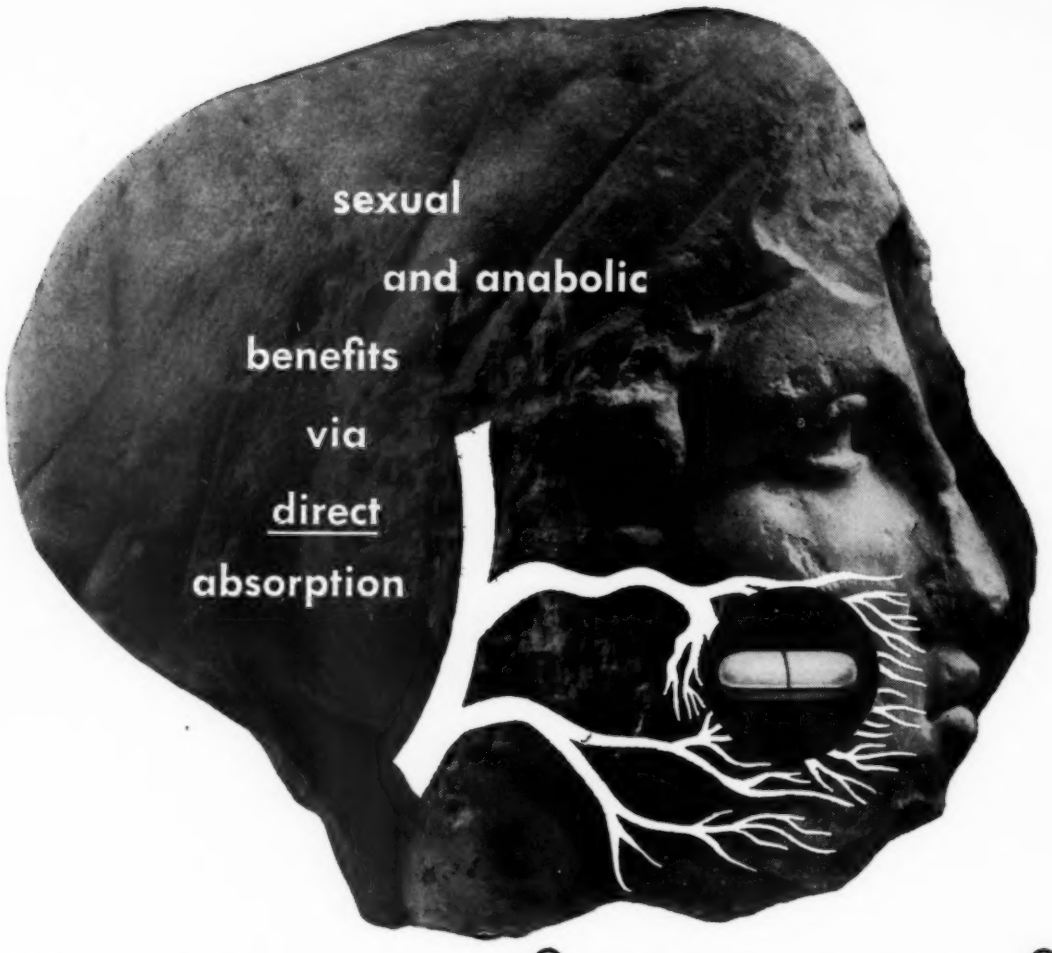

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EFFECT OF CORTISONE ON REACTIVATED METASTATIC CARCINOMA OF PROSTATE

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INTRODUCTION

The frequently beneficial effect, both subjective and objective, of reducing androgenic activity in patients with metastatic carcinoma of the prostate by bilateral orchiectomy and estrogen is well known (Huggins *et al.*, 1, 2). Eventually, however, the carcinoma becomes reactivated. Scott and Vermeulen (3) showed that the fall in 17-ketosteroid excretion which follows orchiectomy is soon followed by a rise to normal or supernormal levels. Huggins and Scott (4) postulated that reactivation of the carcinoma is due to androgen escape, and therefore they removed the adrenals bilaterally as the only remaining source of presumed androgen. Bilateral orchiectomy or estrogen administration has been found to result in adrenocortical hypertrophy in a variety of rodents (5, 6). It is interesting, by way of apparent contrast, that none of the bilaterally adrenalectomized patients of Huggins and Scott showed adrenal hypertrophy, even though they had become refractory to bilateral orchiectomy and estrogen and were in the younger old-age bracket (45 to 60 years). This observation has been corroborated by the results of numerous autopsies on orchiectomized patients. Conclusive evidence that the normal adrenal glands manufacture androgen is wanting. Farrell and Lamus (7) and Farrell (8) did not report increased concentration of androgen in adrenal venous blood, although they noted increased concentration of 17-hydroxycorticosterone, corticosterone, and of 11-desoxy-17-hydroxycorticosterone in such blood. Talbot *et al.* (9) found that there are distinct qualitative differences between the 17-ketosteroid mixtures excreted by patients with adrenocortical virilism and by normal persons. They pointed out that normal adrenocortical 17-ketosteroid precursors may not be androgenic even when excreted in large amounts, whereas abnormal 17-ketosteroid precursors may be androgenic when excreted in relatively small amounts.

The questions remain: Is reactivation of prostatic carcinoma, after protracted control and remission by orchiectomy and estrogen, the result of a compensatory increase of adrenocortical activity? Is the described rebound of 17-ketosteroid

TABLE 1

Case No.	Reg. No. & Age	Symptoms	Local lesion	Metastases	Serum acid phosphatase (K-A units/ 100 cc.)	Serum alk. phosphatase (Bod. units/ 100 cc.)	Blood Hb	Urinary 17-KS (mg./24 hrs.)	Urinary 11-oxy-CS (mg./24 hrs.)	Therapy	Remarks
1	31,332 63 yrs.	Unimproved	Increased	Increased rapidly	8.8→10.8	6.1→13.1	Decreased	—	—	Orchiectomy & stilbestrol (2½ mo.)	Radioactive gold had been injected into prostate before evidence of metastases. Transurethral resection preceded orchiectomy for 145 cc. residual.
		Much increased	Increased	Increased rapidly	11.0→37.5	16.9→ 7.4	Decreased	5.96→4.69	3.45→5.93	Cortisone, 25 mg. b.i.d. (2 mo.)	No stilbestrol. Died in cachexia.
2	30,002 61 yrs.	Increased	Same	Increased rapidly	20.8→8.5→18.0	15.8→46.4→35.5	Decreased	2.36→2.19	3.33→6.01	Cortisone, 25 mg. b.i.d.; stilbestrol, 5 mg. daily (3 mo.)	Died in cachexia.
3	23,150 67 yrs.	Unimproved	Same	Slowly but constantly increased	13.5→11.6	5.2→7.4	Constant	0.69→3.05	2.65→27.6	Cortisone, 25 mg. b.i.d.; stilbestrol, 5 mg. daily (4 mo.)	Alive and well.
4	40,198 59 yrs.	Improved	Reduced	Constant (proved by biopsy at laminectomy)	1.4→1.4	1.9→2.0	Constant	10.3→4.4	8.4→17.64	Cortisone, 25 mg. b.i.d.; stilbestrol, 5 mg. daily (2 mo.)	
		Same	Same	Accelerated	1.0	2.5	Constant	3.60 (initial)	14.75 (initial)	Cortisone, 50 mg. b.i.d.; stilbestrol, 5 mg. daily	Mercuhydrin administered because of weight-gain and minimal congestive failure.
		Same	Same	Same	1.5	3.7	Constant	3.80	3.68	Cortisone, 25 mg. b.i.d.	Cortisone alone for two months immediately following. Alive and well.
5	38,056 58 yrs.	None	Markedly decreased	Increased	6.4→3.4	43.2→43.4	Decreased	—	—	Orchiectomy + stilbestrol, 5 mg. daily	Hemiplegia, left, from old CV accident.
		Improved	Constant	Increased	5.5→4.9	28.2→27.7	Decreased	6.82 9.65 4.17	6.53 3.18 5.39	Cortisone, 50 mg. b.i.d.; stilbestrol, 5 mg. daily (2 mo.)	
		Severe pain in hips	Increased	Increased	4.8	45.2	Decreased	4.57 (3 wks.) 4.42 (2 mo.)	10.19 (3 wks.) 6.38 (2 mo.)	Cortisone alone, 25 mg. b.i.d. (2 mo.)	Died of CV accident one month after cessation of therapy.
6	33,665 57 yrs.	Same	Constant	Extensive metastases (no obvious improvement)	3.2→2.6	10.4→7.6	Constant	8.8	2.82	Cortisone, 25 mg. b.i.d.; stilbestrol, 5 mg. daily	Alive and paraplegic from vertebral metastatic damage.
7	26,375 64 yrs.	None	Decreased	Increased	3.3 3.2 1.3 (2 wks.) 2.8 (2 mo.)	6.0 5.9 6.3 (2 wks.) 6.8 (2 mo.)	Decreased	4.65 16.16	11.2→7.70	Cortisone, 50 mg. b.i.d.; no stilbestrol (2 mo.)	Died in cachexia and sepsis from pulmonary abscesses one month after therapy.

excretion after orchiectomy the cause of the reactivation? This rebound did not occur even after twenty-four months in the patients of Harrison *et al.* (10), who were given estrogen along with orchiectomy. These investigators could not correlate reactivation of the carcinoma with a rise in 17-ketosteroid excretion. However, they do not consider 17-ketosteroid excretion to be an accurate measure of adrenocortical activity. We, therefore, in this pilot study, sought to reduce adrenocortical activity by physiologic means, in order to note the effect on metastatic carcinoma of the prostate which had become refractory to orchiectomy and stilbestrol. We accomplished this by administering cortisone orally in two daily doses (*see* section on excretion of 17-ketosteroids).

RESULTS

Seven cases of metastatic carcinoma of the prostate were studied and the data are listed in Table 1.

Symptoms. Pain secondary to metastasis was temporarily diminished in 2 cases (Nos. 4 and 5; *see* Table 1). In one of these (No. 5) the amelioration lasted only two months, after which the pain became most severe with continued cortisone therapy. One patient (No. 7) had never had pain and died in cachexia one month after cortisone. In 2 cases (No. 1; and terminally, No. 5) the pain greatly increased during cortisone therapy. Three showed no change (Nos. 2, 3, and 6). Appetite tended to be inversely proportional to pain.

Local lesion. The prostatic lesion was markedly augmented in 2 cases (Nos. 1 and 5); it was unchanged in 5 cases; and it diminished in 2. It is interesting that regression of the local lesion but extensive increase in metastases followed

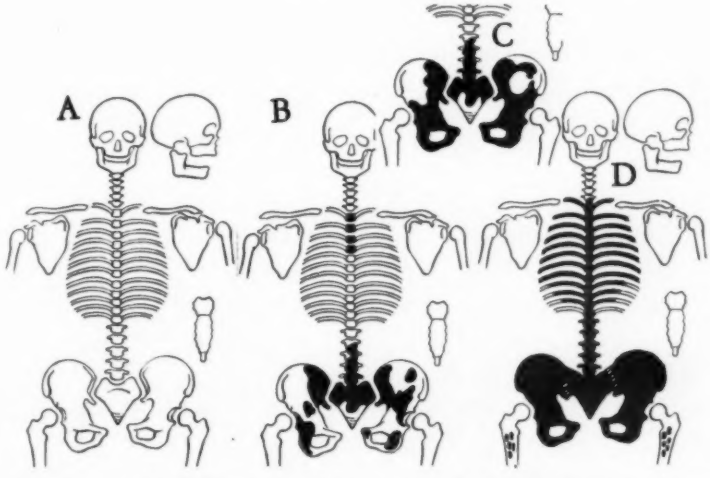

FIG. 1.* *Case No. 1* (#31,332). **A.** October 1953; before orchiectomy and stilbestrol. **B.** February 1954; just before cortisone. **C.** March 1954; after one month of cortisone. **D.** April 1954; after two months of cortisone.

* Diagram of skeleton is from Albright, F., and Reifenstein, E. C., Jr.: The Parathyroid Glands and Metabolic Bone Disease. Baltimore, The Williams & Wilkins Co. (with permission of the publishers).

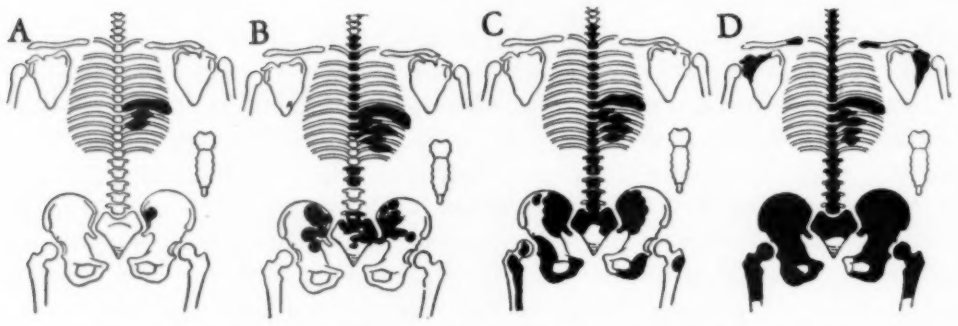

FIG. 2. *Case No. 2* (#30,002). **A.** December 1952; three months before orchiectomy and stilbestrol. **B.** June 1953; just before cortisone. **C.** After seven weeks on cortisone. **D.** After three months on cortisone.

orchiectomy and stilbestrol in No. 5; yet cortisone failed to maintain regression of the prostatic lesion or reduce the rate of spread of the metastases to bone.

Metastases to bone. In no case was there regression or apparent arrest of metastases to bone (Figs. 1 to 5).

Serum acid phosphatase. In 2 cases (Nos. 1 and 3) there was an appreciable increase in the already elevated serum acid phosphatase level. In 2 cases (Nos. 2 and 5) there was no significant change in the already elevated level, despite the rapid increase of metastases to bone. In 3 cases (Nos. 4, 6 and 7) the concentration of acid phosphatase remained normal, although in Nos. 6 and 7 there were highly advanced metastases to bone (Figs. 4 and 5). There was no decline of elevated serum acid phosphatase levels under cortisone therapy.

Serum alkaline phosphatase. The serum alkaline phosphatase level rose significantly in Case No. 2, paralleling an extensive increase in osteoblastic metastases (Fig. 2). This rise, however, was conspicuously absent in the other cases, all of which showed striking radiographic evidence of augmented osteoblastic activity.

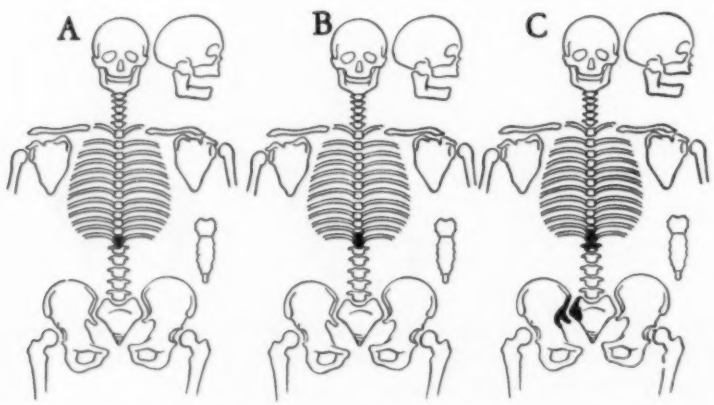

FIG. 3. (#40,198). **A.** September 1953; before cortisone and stilbestrol. **B.** December 1953; after two months on cortisone and stilbestrol. **C.** February 1954; after 100 mg. cortisone and 5 mg. stilbestrol daily for two months.

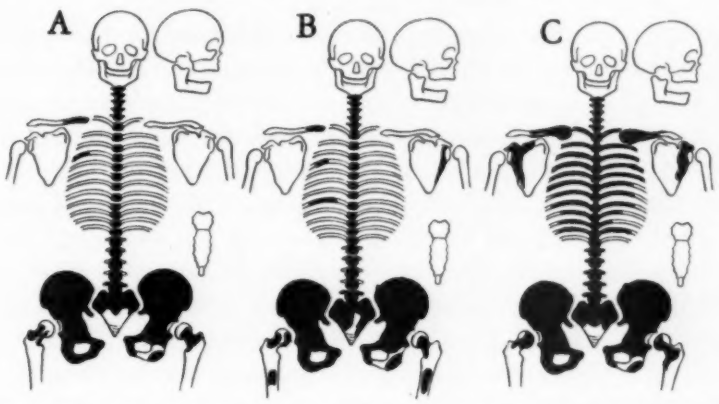

FIG. 4 (#33,665). **A.** April 1952; before orchiectomy. **B.** October 1952; five months after orchiectomy and stilbestrol. **C.** June 1953, before cortisone. Two months after cortisone there was no obvious change.

Hemoglobin. The hemoglobin concentration of the blood decreased in 4 cases (Nos. 1, 2, 5 and 7). This decrease was not associated with bleeding, such as would occur with transurethral resection. The other 3 cases showed no changes in the hemoglobin level. Devastating metastases to bone do not necessarily imply anemia, although anemia, when present, invariably is associated with them. Thus Patient No. 6 had involvement of the entire spine and girdles, but was not anemic. Anemia is a grave prognostic sign. All the anemic patients died within a few months, whereas the others still survive.

Total 17-ketosteroids. The general trend was toward a significant drop in daily urinary 17-ketosteroid excretion during cortisone therapy (Table 1). The abnormally low initial value of 0.69 mg. for Case No. 3 was probably at least partly due to an incomplete urinary collection. On the whole, the 17-KS outputs dropped to a low minimum during cortisone therapy. We cannot explain with certainty the final high value of 16.16 mg. in Case No. 7. This patient was re-

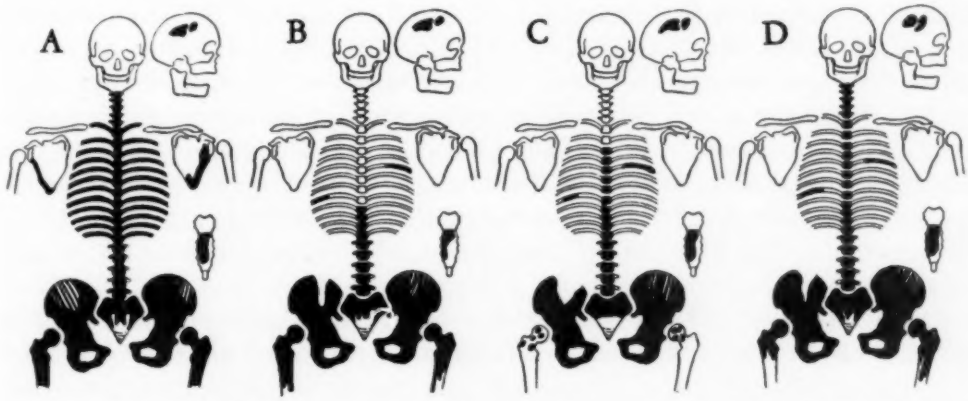

FIG. 5. (#26,375). **A.** May 1952; just before orchiectomy and stilbestrol. **B.** February 1953; just before cortisone. **C.** April 1953; after six weeks on cortisone. **D.** May 1953; after three months on cortisone.

ceiving 100 mg. of cortisone daily and no stilbestrol (*see* Discussion). On the other hand, Patient No. 5, who showed a drop in 17-KS excretion was also receiving 100 mg. of cortisone daily and 5 mg. of stilbestrol in addition. The 17-KS excretion was not abnormally high, even for aged men, at the time of exacerbation of the carcinoma. From this standpoint there was, therefore, no evident correlation of reactivation of carcinoma with increased adrenocortical activity.

Total 11-oxycorticosteroids. The 24-hour urinary excretion of 11-oxycorticosteroids definitely tended to increase during cortisone therapy. Case No. 7 is again puzzling, because the 11-oxycorticosteroid excretion fell; thus neither the 17-KS nor 11-OCS behaved as expected. There is no doubt about the accuracy of these urinary collections.

DISCUSSION

Symptoms. Relief of pain of metastatic origin has been noted frequently after bilateral adrenalectomy for carcinoma of prostate or breast (11–14). With subsidence of pain there is often increased activity, improved appetite and, more seldom, a gain in weight and a rise in the blood hemoglobin level. Huggins and Bergenstal (11) and West *et al.* (12) affirm that subjective improvement after adrenalectomy is much greater than that observed in the same patients during cortisone or ACTH therapy before adrenalectomy. This tends to be confirmed by Miller and Hinman (15). The reason is unknown.

Hayward (16), Valk and Owens (17), and Miller and Hinman (15) have noted relief of pain with improved appetite and weight gain in some patients with relapsing metastatic prostatic carcinoma when treated with cortisone, 25 to 100 mg. daily in divided doses. Two of our 7 patients realized this benefit, although in 1 it was for only two months in spite of continued cortisone therapy.

Local lesion. Valk and Owens (17) found no change during cortisone therapy in the local lesion of 12 patients with relapsing carcinoma of the prostate. On the other hand, 6 of 10 cases reported by Miller and Hinman showed moderate to marked improvement on rectal palpation. In 3 there was complete disappearance of palpable prostatic tissue; in 1 case an initial unilateral hydronephrosis cleared under cortisone. Huggins and Bergenstal (11) reported a local diminution of the prostatic cancer in 2 of 6 bilaterally adrenalectomized patients with metastatic carcinoma of the prostate. West *et al.* (12) had only 1 such local regression among 10 bilaterally adrenalectomized patients. In our small series there was local regression in 2 cases out of 7 during cortisone therapy. So far as we know, nobody has reported on the local histologic picture after cortisone or bilateral adrenalectomy.

Metastases to bone. Dramatic evidence of objective improvement would be presented by radiograms showing metastatic regression such as has been noted many times after orchiectomy and estrogen. So far as we are aware the only evidence of such regression which may be ascribed to cortisone or bilateral adrenalectomy is a case of Harrison *et al.* (10). Even in that patient, however, the change may have been merely from an osteoclastic to an osteoblastic metastatic lesion.

Serum acid phosphatase (SAP). Valk and Owens (17) reported a fall in the serum acid phosphatase level in 8 of 12 cases during cortisone therapy. Miller and Hinman (15) noted that 3 of the 4 patients with initially elevated serum acid phosphatase levels showed a decrease in SAP under cortisone. In 2 patients the SAP rose, yet both had symptomatic relief and regression of their local lesion. Huggins and Bergenstal (11) observed a fall in SAP concentration in 2 of the 6 bilaterally adrenalectomized patients in whom it had been elevated. West *et al.* (12), on the other hand, noted no significant or protracted decrease in the SAP concentration in 10 patients with metastatic carcinoma of the prostate who underwent bilateral adrenalectomy. Baker *et al.* (13) found no decline in elevated acid phosphatase levels after bilateral adrenalectomy. None of our cases showed a decrease in an abnormally elevated SAP level during cortisone therapy.

Excretion of total 17-ketosteroids. Since our patients were bilaterally orchiectomized their adrenal glands were the source of all or practically all of the initial urinary 17-ketosteroid (4, 18). Their urinary 17-ketosteroid values may thus be used as a rough gauge of adrenocortical activity. Our ideal was to obliterate adrenocortical activity by physiologic means and yet not give too much of the obliterating agent to be a disturbing factor. Cortisone administration, by inhibiting the production of pituitary adrenocorticotropic hormone, results in diminished adrenocortical activity and a depression of urinary 17-KS output (19). During prolonged cortisone therapy patients often show atrophic adrenal cortices at autopsy, and patients with a hyperfunctioning tumor of the adrenal cortex are likely to have an atrophic contralateral adrenal cortex. Wilkins *et al.* (20–23) suppressed androgen secretion by cortisone in patients with congenital hyperplasia. They found 50 mg. of cortisone daily adequate to induce full suppression of adrenocortical hyperactivity in adults, as indicated by the total 17-KS excretion. Suppression of 17-KS excretion occurred more rapidly with oral than with intramuscular administration. They found no difference between the effects of 25 mg. twice daily and 12.5 mg. four times daily. Thorn *et al.* (24) found 50 mg. of cortisone optimal in decreasing urinary 17-KS. Harrison *et al.* (10) reported a fall in urinary 17-KS in 9 orchiectomized patients with metastatic carcinoma of the prostate receiving 25 to 37 mg. of cortisone daily. The fall was typically from 10 mg. to 6 mg. per twenty-four hours. It is interesting that the latter value is close to that observed in bilaterally adrenalectomized and orchiectomized patients receiving a maintenance dosage of cortisone with estrogen (10).

Valk and Owens (17) noted a fall in the excretion of 17-KS in 7 of 9 patients with metastatic carcinoma of the prostate receiving 50 mg. of cortisone daily. The 17-KS excretion rose in the other 2 cases. Miller and Hinman (15) reported similar findings and noted no correlation between the fall in 17-KS and the clinical improvement. In this connection it may be significant that Harrison *et al.* (10) found no consistent correlation between the rise in 17-KS and the reactivation of the carcinoma after orchiectomy and stilbestrol. In our cases there was a definite tendency for the urinary 17-KS to fall during cortisone therapy (50 to 100 mg. daily). Cases in which there was rapid deterioration to carcinoma showed striking falls (Nos. 2 and 5) but so did cases which remained almost stationary (Nos. 3 and 4).

When a dose of 50 mg. of 17-hydrocorticosterone is given orally, this compound reaches a peak concentration in the blood in from forty-five to sixty minutes and falls to normal in from four to six hours (25). A small fraction (1.5 to 4 per cent) of the administered cortisone appears in the urine as 17-KS (26–28) and thus probably distorts the picture of adrenocortical activity, especially when large doses of cortisone are given.

Excretion of total 11-oxycorticosteroids. The basal urinary excretion of 11-oxycorticosteroids is much lower than that of 17-ketosteroids, and as great or even greater a component of administered cortisone appears in the urine as 11-OCS than as 17-KS (9, 28). Changes in urinary excretion of 11-oxycorticosteroid therefore are more of a reflection of the administered cortisone than of adrenocortical activity. Thus Miller and Hinman (15) noted a rise in the corticosteroid excretion of all 10 patients who were being treated with cortisone. In our cases 11-oxycorticosteroid excretion tended to rise during cortisone therapy.

SUMMARY

Sufficient cortisone to inhibit production of adrenocorticotropic hormone by the hypophysis was administered to 7 patients with metastatic carcinoma of the prostate which had become refractory to bilateral orchiectomy and stilbestrol. The only improvement observed was temporary diminution in pain of metastatic origin in 2 cases and recession of the local lesion in 1 case.

The pertinent literature on the subject is discussed.

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STEROID STUDIES. III. THE INFLUENCE OF ANABOLIC STEROIDS ON THE CHROMATOGRAPHIC PATTERNS OF 17-KETOSTEROID EXCRETION BY HYPOGONADAL AND AGED MEN*

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Androsterone and etiocholane-3(α)-ol-17(β)-one are well documented as the major urinary excretion products of the *in vivo* metabolism of testosterone (1–15). Most of these studies have involved young adults of both sexes. The oldest human subject in whom partition chromatography of the urinary neutral 17-ketosteroids has been carried out following the administration of testosterone appears to have been 43 years old (14). Chromatographic patterns of the neutral 17-ketosteroids in men over 50 rarely have been reported (16–18).

As far as we can determine, no studies of the chromatograms of the urinary neutral 17-ketosteroids have been made following the administration of androstan-17(β)-ol-3-one (stanolone) to human beings. However, this compound has been shown to possess "anabolic" properties similar to those of testosterone (19–22).

The excretion patterns of the urinary neutral 17-ketosteroids of aging men have been described elsewhere (23). These have been compared with those of younger men and of hypogonadal subjects and eunuchs. In such analyses it has been observed that in both hypogonadal and aging subjects there is a diminution in the amount of material isolated in that portion of the chromatogram in which androsterone appears, and an increase in the fractions containing etiocholanolone. The present study is devoted to ascertaining the influence of testosterone and stanolone upon such chromatograms.

METHODS AND PROCEDURES

The data were obtained from studies with 7 men, including 4 aged subjects who were 58, 63, 70 and 75 years old; 2 hypogonadal subjects, 63 and 67 years old; and 1 agonadal male, aged 43 years.

In these men, the total neutral urinary 17-ketosteroids were in each instance extracted from an aliquot of the urine excreted in a 24-hour period or some whole multiple thereof, by the method of Drekter *et al.* (24). In Figure 1 is illustrated the type of chromatogram obtained. The steroids were chromatographed over an alumina column, which was developed by 25-ml. portions of benzene, 0.1 per cent ethanol in benzene, 0.5 per cent ethanol in benzene, and absolute ethanol, in accordance with the method of Wilkins and Carlson (25). Forty-four fractions were obtained. The 17-ketosteroid content of each fraction was measured by the

* Read in part before the Third International Gerontological Congress, London, England, July 23, 1954.

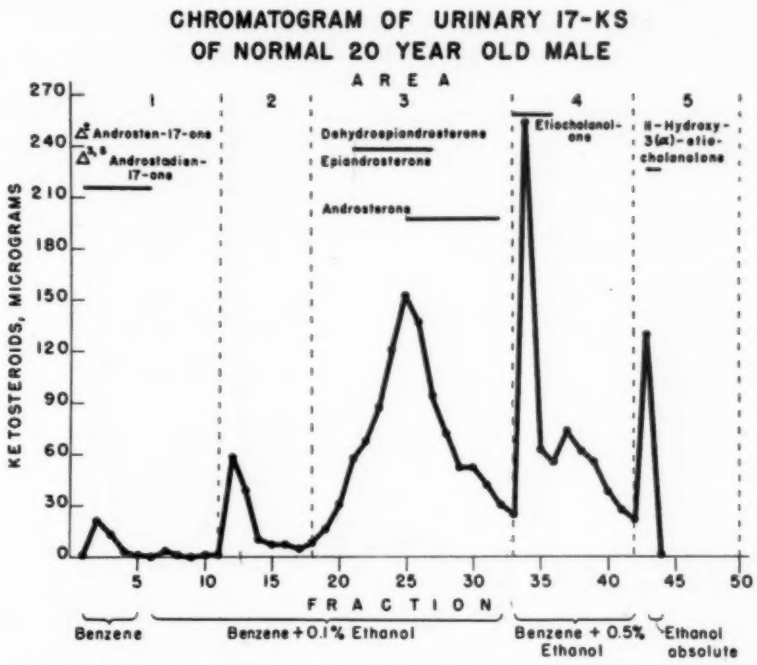

FIG. 1. (Heavy horizontal lines at the top of the graph illustrate the area in which the corresponding pure compounds are eluted from the column. The vertical dotted lines separate the graph into areas in relation to the five major peaks of eluate obtained.)

Zimmermann reaction and the ketosteroid content was plotted against the number of the fraction as it came off the column. Each chromatogram was divided into five areas. The eluates from each area contained a different steroid or group of steroids. That fraction which contained more ketosteroids than the preceding fraction was taken as the starting point for a new area, on the assumption that the rise in ketosteroids indicated the point at which one steroid or group of steroids had been eluted from the column and another group of steroids began to appear in the eluates. Despite the fact that this assumption was often an approximation, the data obtained were extremely useful. The sum of the ketosteroids in the fractions which were found in each area is a quantitative measure of a group of steroids.

The urinary neutral 17-ketosteroids of 3 normal men, 20 to 21 years old, were chromatographed for comparison with the patterns obtained in the 7 men who were the main subjects of the present study.

On the basis of our work and that of other investigators, it may be concluded that some artefacts are present in area 1. Epiandrosterone and androsterone, the precursors of which are assumed to be primarily of gonadal origin, are eluted in area 3. In area 4 is found etiocholan-3(α)-ol-17-one, the precursors of which are believed to have their origin in both the gonads and the adrenal cortex. In the fifth and final region of the chromatogram are 11-oxygenated steroids, probably of adrenocortical origin. At least the pure steroid, 11-hydroxy-3(α)-etiocholanolone is eluted from the column in this area. The steroids of area 2 have not been

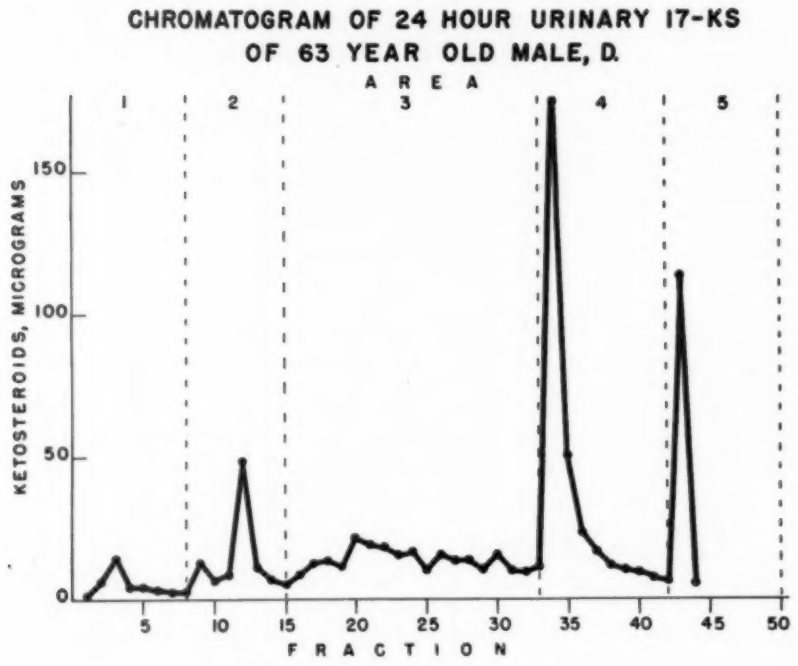

FIG. 2. (See Fig. 1 for key).

fully defined but we believe that most of their precursors originate in the adrenal cortex.[1]

Control chromatograms were developed from the extracts of 24-hour specimens of urine, or from whole multiples thereof, in 3 young men; in the 4 "normally aging" subjects to a total of 10 patterns; and in the 3 men with long-standing disturbances of gonadal function to a total of 8 studies. In Figure 2 is represented the chromatogram from a normally aging man. This is to be contrasted with the chromatogram in Figure 1. There is loss of steroids in area 3, where androsterone commonly appears. Following these control studies (some of which were several weeks apart) stanolone or testosterone, or each in succession, was administered to the 5 individuals, and chromatograms were again made at daily or other appropriate intervals during the period of administration, and for short periods following the discontinuance of the steroid.

RESULTS

In Figure 3 is a schematic representation of the control chromatograms of the three different groups of men. It is particularly noteworthy that the percentage of the total excretion of the young men is highest in the region of elution of androsterone, and nearly as high in the area of the appearance of etio-

[1] Pure compounds for control chromatograms were made available through the courtesy of: Dr. E. E. Henderson, Schering Corporation, Bloomfield, N. J. (dehydroepiandrosterone, epiandrosterone, 11-hydroxyetiocholanolone); Dr. J. B. Jewell, Ayerst, McKenna & Harrison, Ltd., New York, N. Y. (androsterone); and Dr. Seymour Lieberman, Columbia University, New York, N. Y. (etiocholanolone).

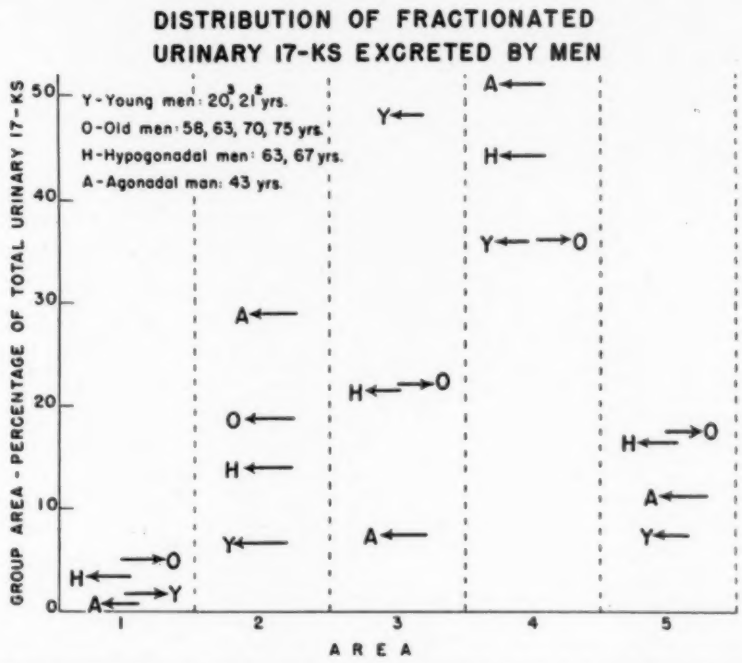

FIG. 3. The percentage distribution of the material eluted from the alumina column, according to the clinical condition of the subjects. In each instance the horizontal bar represents the percentage of total material eluted in the corresponding area for the designated group.

cholanolone, the ratio of area 4 eluate to area 3 eluate for the 3 subjects being 0.77. In the aged this ratio increases considerably, and if we exclude W, who showed an excretion pattern not unlike that of the young men (Table 2; Fig. 5), this ratio becomes 1.6. The ratio for the hypogonadal individuals is 1.9 and for the agonadal male, 6.2.

With these facts in mind, it is pertinent to review the influence of stanolone and testosterone in doses of varying size and frequency upon the pattern of excretion of the old men on the one hand and those with decreased testicular

TABLE 1. *The Effect of Daily Dosage of 100 Mg. of Androstanolone upon the Amount and Composition of 24-hour Neutral Urinary 17-Ketosteroids of a 63-year-old Male*, **D**

Days	Total dosage (mg.)	Av. 24-hr. 17-KS excretion (mg.)	17-KS (μg.)				
			Area 1	Area 2	Area 3	Area 4	Area 5
1–3	0	13.3	36	105	230	307	118
4–6*	200	13.6	49	254	305	140	52
7–9	500	19.1	18	88	806	131	101
10–12*	700	23.3	96	180	831	167	116
13–15		14.3	—	—	—	—	—
16–18		12.4	34	168	399	102	89

* Injections were started on the fifth day and ended on the eleventh day.

activity on the other. At the outset, it should be emphasized that all of the subjects with decreased or absent sexual function had had their disturbances from the time of early adolescence. Further attention should be called to the fact that 2 of these patients were in the same range of age as 3 of our "aged" subjects. (Tables 3, 5 and 6; Figs. 6, 8 and 9).

TABLE 2. *The Effect of Daily Injections of 100 Mg. of Androstanolone upon the Amount and Composition of 24-hour Neutral Urinary 17-Ketosteroids of a 70-year-old Male,* **W**

Days	Dosage (mg.)	Av. 24-hr. 17-KS excretion (mg.)	17-KS (μg.)				
			Area 1	Area 2	Area 3	Area 4	Area 5
1–3	0	8.4	57	277	992	460	199
4–6*	200	12.9	61	540	836	311	37
7–9	500	14.0	122	242	1164	317	140
10–12	700	19.3	125	751	1399	311	228
13–15*	800	21.0	183	344	2111	844	666
16–18		18.1	74	391	1531	227	187
19–21		6.2	54	221	1258	275	177
22–24		5.6	33	246	1266	284	154

* Injections were started on the fourth day and continued through the thirteenth day. No injection was given on the fifth and tenth days.

TABLE 3. *Influence of Stanolone upon the 24-hour Neutral Urinary 17-Ketosteroids*

C, ♂, (agonadal), 43 years

Days	Total dosage (mg.)	Av. 24-hr. 17-KS excretion (mg.)	17-KS—μg. in Areas				
			1	2	3	4	5
1–2	0	7.8	17	578	152	1017	225
9–15*	450	19.0	538	802	2655	338	364

* Intramuscular injections of 50 mg. of stanolone were started on the fifth day.

TABLE 4. *Influence of Testosterone Propionate upon the 24-hour Neutral Urinary 17-Ketosteroids*

D, ♂, 63 yrs.

Days	Total dosage (mg.)	Av. 24-hr. 17-KS excretion (mg.)	17-KS μg. in Areas				
			1	2	3	4	5
1–3	0	13.3	36	105	230	307	118
13–15		14.3	—	—	—	—	—
16–18		12.4	34	168	399	102	89
19	100	32.1	88	237	988	466	146
20	200	51.6	16	1053	1049	893	101
21	300	51.0	11	115	2328	447	127
22	400	70.6	—	—	—	—	—
23	500	72.0	42	176	2269	1597	223

TABLE 5. *Influence of Testosterone Propionate upon the 24-hour Neutral Urinary 17-Ketosteroids*

M, ♂, (hypogonadal), 63 yrs.

Days	Total dosage (mg.)	Av. 24-hr. 17-KS excretion (mg.)	17-KS—μg. in Areas				
			1	2	3	4	5
1–3	0	7.4	75	396	309	919	291
4–6*	50	12.0	92	429	1896	571	238

* Testosterone propionate (50 mg.) was injected on the fourth day.

TABLE 6. *Influence of Testosterone Propionate upon the 24-hour Neutral Urinary 17-Ketosteroids*

S, ♂, (hypogonadal) 67 yrs.

Days	Total dosage (mg.)	Av. 24-hr. 17-KS excretion (mg.)	17-KS—μg. in Areas				
			1	2	3	4	5
1	0	6.3	66	184	530	832	374
2	50	19.4	237	825	1910	2664	489

The chromatographically separated fractions of steroids excreted before and after administration of stanolone to D, the 63-year-old man, were compared (Table 1; Fig. 4). The first two injections (200 mg.) resulted in an increased excretion of the steroids in areas 1, 2 and 3 (Table 1). On the basis of previous work, area 2 probably contains steroids primarily of adrenocortical origin; and androsterone, epiandrosterone and dehydroepiandrosterone are found in area 3. With continued administration of stanolone the amount of steroids in area 2 decreased, increased and finally approached the control value in the fifth, sixth and seventh days of the recovery period (sixteen to eighteen days of study). In this same period the amount of ketosteroids found in area 3 remained high, although there was a decrease after the last injection on the eleventh day of the study. Apparently over 90 per cent of the metabolites of stanolone appeared in area 3, the region in which epiandrosterone and androsterone are found.

If endogenous formation of urinary 17-ketosteroids remained constant before and after the injections of stanolone, the urinary steroids excreted after the injections should consist of the same endogenous steroids excreted before the injections plus metabolites, and no area should contain fewer steroids after stanolone was given than before the injections. It was found that area 4, the region in which etiocholanolone appears, did show a decreased ketosteroid content after the administration of stanolone. Therefore, the injection of the steroid did alter the endogenous formation of 17-ketosteroids or some endogenous factor which affects the composition of urinary neutral 17-ketosteroids.

The composition of the urinary 17-ketosteroids changed before any increase in total ketosteroid excretion was found (Table 1, days 4–6) and remained altered after the total daily urinary neutral 17-ketosteroid excretion had returned to normal (days 16 to 18). It would seem that the chromatogram may

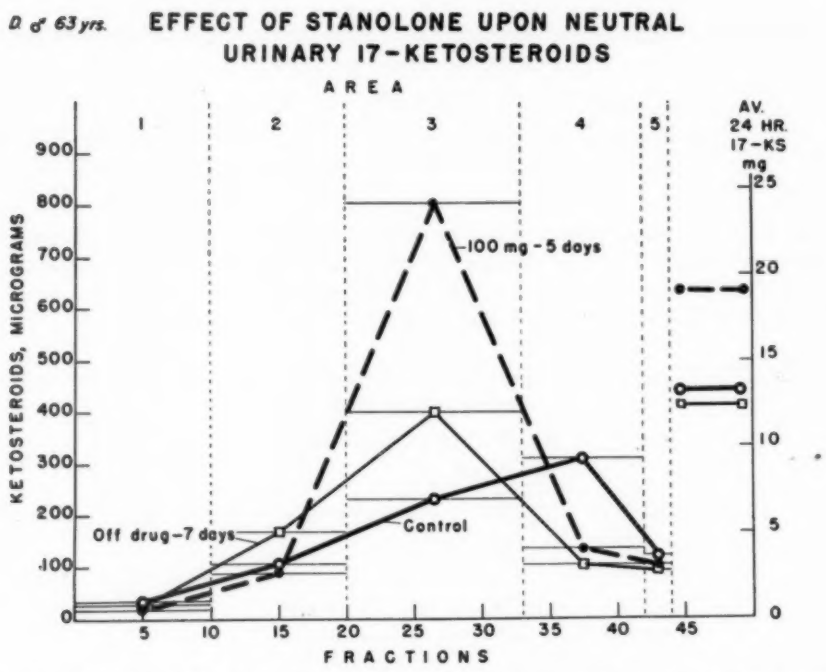

FIG. 4. (The horizontal bars represent the amount of material excreted in the designated area. The linear graph enables the reader to follow easily the effects of each level of steroid administration).

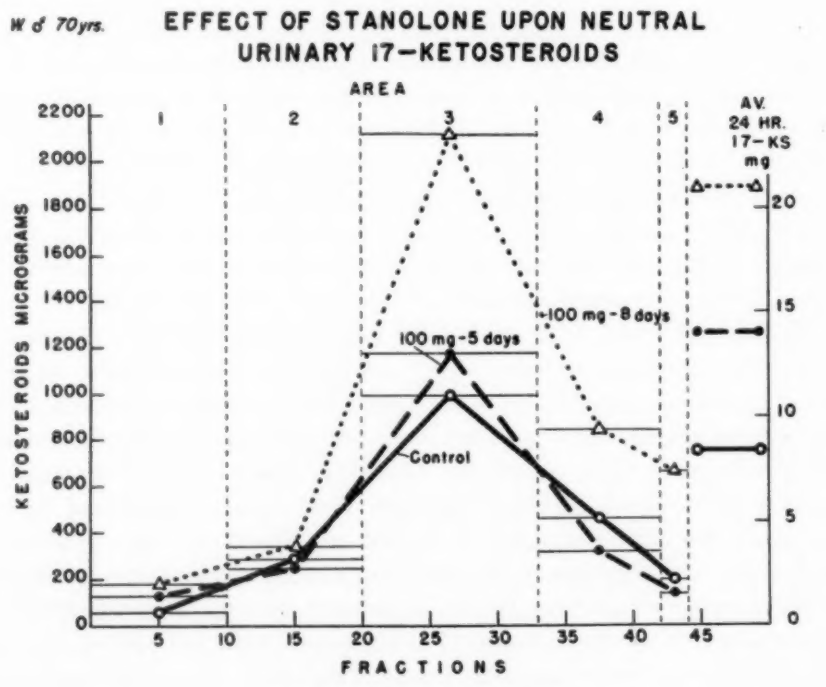

FIG. 5. (See Fig. 4 for key.)

provide a more sensitive method for following changes which accompany aging and the response of the aged to steroid therapy than does the measurement of total daily urinary neutral 17-ketosteroids.

W, a 70-year-old male with generalized arteriosclerosis, was also given daily intramuscular injections of 100 mg. of stanolone. His response resembled that of D in the increase in daily urinary 17-ketosteroids, the alternate increase, decrease and increase in the amount of steroids in area 2, and the increase in the steroids in area 3 (Table 2, Fig. 5), but there were several points of difference. The rise in the 24-hour excretion of urinary 17-ketosteroids shown by W after injections of stanolone occurred sooner than that observed in the case of D. Furthermore, there was a more rapid and greater increase in the amount of steroids in area 3 of the chromatogram of D than in the chromatogram of W and there was no decrease in the steroids in area 4 of the chromatogram of W, as was noted in the case of D. These differences may be very important. Similar differences were observed between the effects of stanolone upon the composition of the urinary steroids excreted by W and another patient, C, whose responses also differed from those of W metabolically, clinically, and on the basis of quantitative studies.

C, a 43-year-old agonadal obese male who, upon the basis of testicular biopsy findings, had no functioning testicular elements, reacted differently to treatment with stanolone (Table 3; Fig. 6). For twelve days he received daily intramuscular injections of 50 mg. of stanolone, while following a "reducing" diet of

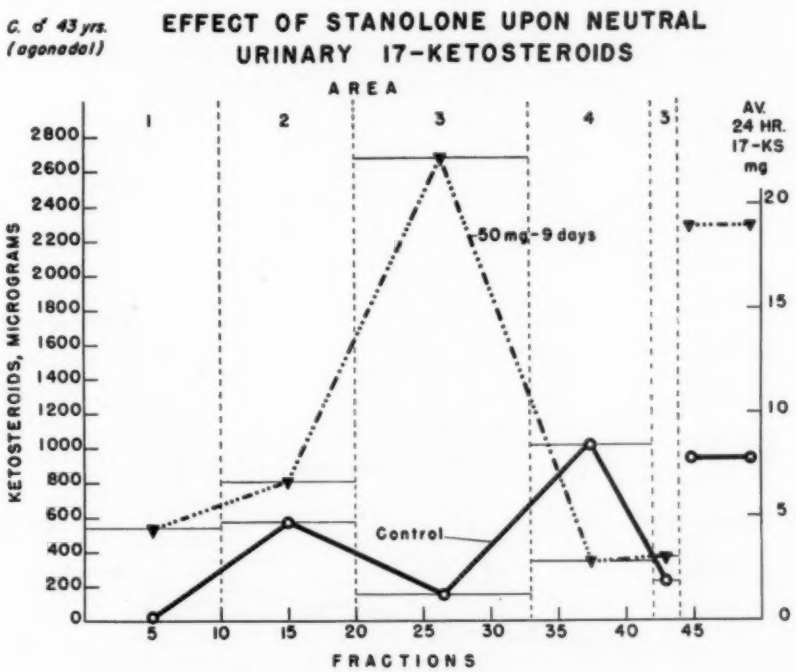

FIG. 6. (See Fig. 4 for key.)

800 calories daily. The administration of stanolone was associated with an increase in the retention of nitrogen, and a marked "feeling of well being."

Comparison of the chromatograms of the urinary 17-ketosteroids excreted before the injections of stanolone were begun and those excreted on the fifth through the thirteenth days of the injections showed that stanolone administration caused a marked increase in the steroids of area 3 and a decrease in area 4 (Table 3), as was noted in the case of D. Patient W, who did not show any change in nitrogen retention, did not excrete less of the steroids found in area 4. This raises the possibility of a correlation between metabolic and clinical effects of a steroid and the effects of the steroid upon the chromatogram of urinary steroids.

Patient **D** was given the first of five daily injections of 100 mg. each of testosterone propionate one week after he received the last dose of stanolone (Table 4; Fig. 7). Unfortunately, the composition of the urinary 17-ketosteroids had not returned to control levels at this time. In evaluating the results, this must be kept in mind. The total 24-hour urinary neutral 17-ketosteroids increased after the first injection (Table 4). In this regard, the response to testosterone differed from the response to stanolone. The increase in urinary 17-ketosteroids was accompanied by a transient rise in the steroids in area 2, a sustained increase in the steroids in areas 3 and 4 and a delayed small increase in area 5. The increases in areas 4 and 5 were not observed after injections of stanolone.

M, a 63-year-old male, was given an intramuscular injection of 50 mg. of

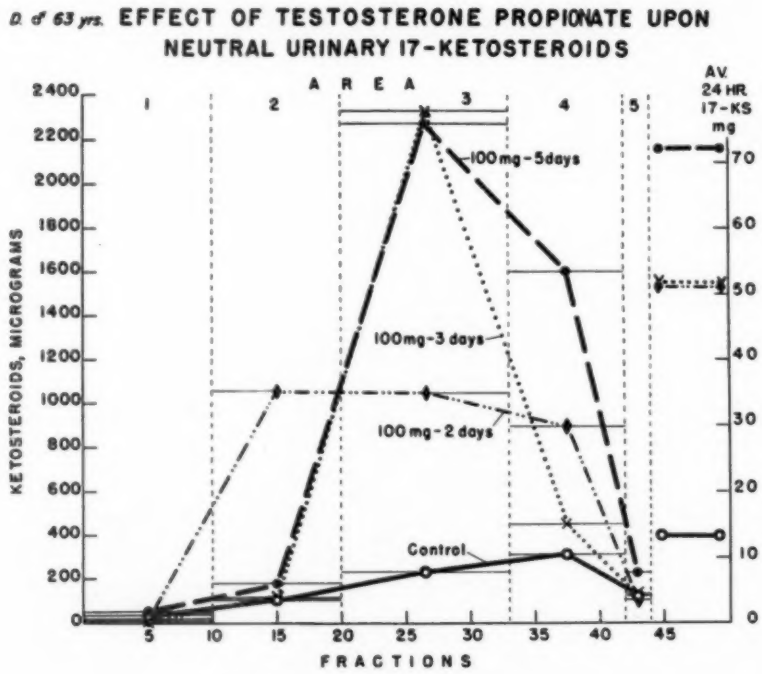

FIG. 7. (See Fig. 4 for key.)

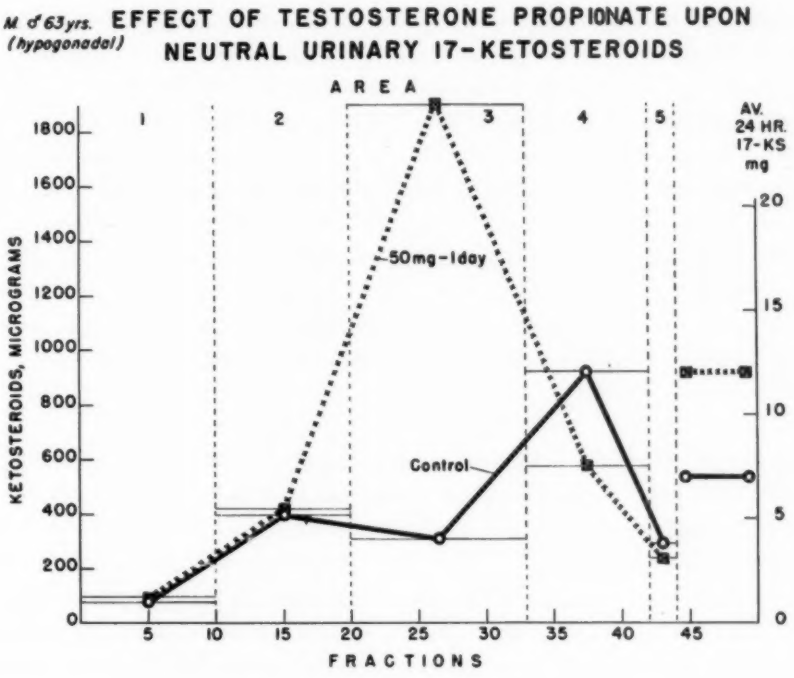

FIG. 8. (See Fig. 4 for key.)

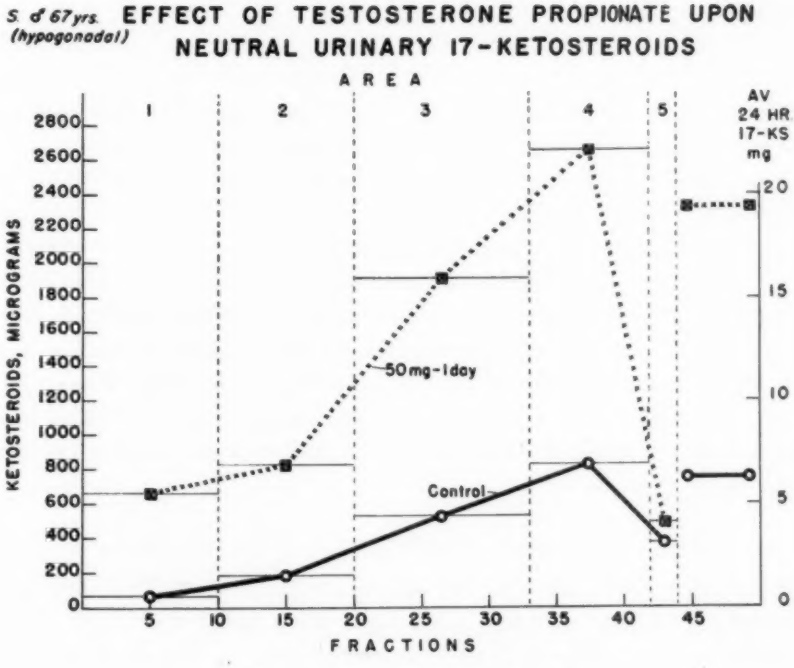

FIG. 9. (See Fig. 4 for key.)

testosterone propionate, and an aliquot of the total neutral 17-ketosteroids excreted in the next seventy-two hours was chromatographed (Table 5; Fig. 8). Comparison with control values showed that the steroids in area 3 had increased and the steroids in area 4 had decreased. This resembled the effects of stanolone in Patients D and C but differed from the effects of testosterone in D, who showed no decrease in the excretion of steroids in area 4 after injections of testosterone.

When **S**, a 67-year-old hypogonadal male, was given a single injection of 50 mg. of testosterone propionate, there was an increase in the total urinary 17-ketosteroids and in the steroid content of areas 2, 3 and 4, as was seen in the case of D (Table 6; Fig. 9). In addition the amount of steroids in area 1 increased.

SUMMARY OF FINDINGS

No significant changes occurred in the amounts of neutral 17-ketosteroids eluted in areas 1 and 5 of the chromatograms in relation to age, status of the testes, or the administration of stanolone or testosterone.

With age or underfunction of the testes there was no change in the absolute amounts of steroids in area 2 of the chromatogram, although the percentage of total excretion was greater in the old, the hypogonadal and the eunuch than in the young man. Both stanolone and testosterone produced a proportionate rise in this fraction which, however, always dropped to a point below the control level during the long-continued administration of the steroid and remained thus depressed after therapy was stopped.

Following the intramuscular injection of a stanolone suspension in water or testosterone propionate in oil (even a single dose), there was always an absolute and percentile increase in the steroid excretion in area 3 of the chromatograms of the aged, hypogonadal and agonadal subjects, which includes fractions containing the bulk of the excreted androsterone. The values for this area remained elevated following the cessation of steroid therapy.

In area 4, where a major portion of the etiocholanolone is found, there was always a percentile decrease in the amount of steroid present as a result of the administration of either stanolone or testosterone propionate, except in subject S (Table 6; Fig. 9), in whom percentagewise there was no significant change. The absolute amounts of material in this region were temporarily increased in 1 of the subjects (W) who received stanolone (Table 2; Fig. 5) and in 2 of the 3 who received testosterone propionate (Tables 4 and 6; Figs. 7 and 9). In all cases in which either drug was continued for more than four days, there was always a secondary decrease below the control levels for at least several days after cessation of treatment.

DISCUSSION

In the present study, the chromatographic patterns of the neutral urinary 17-ketosteroids of aging subjects and those with greater or lesser degrees of gonadal failure had in common one feature not seen in the similarly developed chromatograms of young normal adults. As compared with the normal, these two groups showed a decrease in the steroids found in area 3 and a relatively,

although not always absolute, increase in the amount of material in area 4. It is obvious that there was considerable divergence in the chromatograms from subject to subject, although results of repeated control studies in any given individual, even at widely separated intervals, were in reasonably good agreement with each other.

Stanolone and testosterone both tended to produce chromatograms similar to those of younger individuals. If long continued, testosterone propionate caused an abnormally high amount and proportion of steroids to appear in area 3. Following the use of testosterone-*d*, Fukushima *et al.* (14) found a variation in the ratio of etiocholanolone to androsterone from subject to subject, for which they thought a difference in age might account. They suggested that "the greater transformation of testosterone to the androgenically active compound, androsterone, by the three younger subjects might be considered to reflect a more efficient 'utilization' of this hormone . . .". In summarizing the literature, and adding his own experiences with normal young men and women, Dorfman (13) has called attention to a variation in the 5-beta/5-alpha ratio, *i.e.* the etiocholanolone/androsterone ratio, of from 0.56 to 2.50, but believes this ratio should lie slightly above 1.0 in the average individual. In the 5 young men employed in the present study, an average ratio between the amount of steroidal material in area 4 and area 3 was 0.77, with a variation from 0.21 to 0.90. In the 7 older or hypogonadal individuals made the subjects of this study, this ratio was always above 1.0.

An increase in the androsterone as compared with the etiocholanolone fraction of urinary excretion has been reported by Gallagher and his associates following the intravenous administration of testosterone (15). In aging and hypogonadal subjects this same change appears to occur following the intramuscular use of both this compound and of stanolone.

There are as yet many untried variables which may account for the differences in the chromatograms of subjects of various age groups and of those with altered testicular function. Furthermore, factors must be sought which may account for variations in these patterns in response to "anabolic" steroids. There is no desire to belabor these points. The present studies indicate that:

1. In persons over 60 years of age, and in those who have lowered testicular function, there is a disproportionate decrease in the neutral urinary 17-ketosteroids in the area of the chromatogram where androsterone appears.

2. The administration of either testosterone or stanolone to aged subjects or to hypogonadal men alters the ratio of excreted etiocholanolone and androsterone in the direction of that seen in healthy young men.

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NUTRITION AND AGING*

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The practicing physician is frequently called upon to advise the older patient about his food habits in order to improve his health or to correct some of his complaints. In the present state of our knowledge, we believe that a well-balanced diet of milk, meat, fruits, vegetables and cereals is as important for the individual of 70 years or more as for the child or young adult.

Inadequate funds, the lack of knowledge of food values, and isolation are a vicious combination that makes the older person a ready prey for food faddists. It is surprising and pathetic to witness how eagerly concoctions hinting at the elixir of youth are sought by the older generation. Even the most restricted budget can be stretched to pay for them. The physician who sees an elderly patient should be aware of these factors.

Moderate activity contributes in many ways to the nutrition of an older person, just as it does to that of a younger one. Activity stimulates the circulation, promotes an increased sense of well-being, encourages an interest in food, stimulates a sluggish appetite, and keeps some excess calories from being stored as fat. Improved muscle tonus, a corollary of activity, aids digestion and elimination so that eating is still a pleasure. Bones that are used are the stronger for it.

The elderly patient who must reduce presents a unique problem. Because he often has lived with his excess weight for a long time, he is not easily convinced that its loss may alleviate some more recent complaints or may further improve his chances of surviving.

When an obese elderly patient has arthritis, his activity is likely to be greatly restricted. This minimum of activity results in a minimum caloric expenditure.

In order for such a patient to reduce, a stringent dietary regimen may be necessary. It is important for the subject's morale that the diet result in some weight loss during the first few weeks and a continued loss thereafter. Particular attention should be paid to sodium intake and sufficient limitation should be imposed to prevent the transitory sodium and water retention that often accompanies the first two weeks of a reducing regimen and disguises a real loss of adipose tissue.

Weight loss may be a preventive and therapeutic measure in old age. In formulating a weight reduction program for an aged individual, careful attention must be paid to the selection of nutrients, in order to assure adequate nutrition. For the aged as well as for the young, a weight-reducing diet affords an opportunity for the improvement of food habits. However, it must be recognized that the aged individual does not easily change the food practices of a life time.

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‡ Professor of Nutrition and Chairman, Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts.

Our knowledge of the dietary practices of old people who are not institutionalized is scant, and the majority of elderly people are not institutionalized. In a study of 136 non-institutionalized older women living in the north central region of this country, more than one third were found to be overweight. Obesity and hypertension were the most frequent causes of referral to private physicians in a study in California of more than 500 persons 50 years of age and over. Our department has carefully interviewed a random sample of approximately 100 people over 65 years of age living independently in a low economic area in Boston. We found a mean caloric intake of 2500 ± 1000 for men, and 1700 ± 700 for women. Apparently, the average caloric intake in maturity and old age tends to be greater than the need, resulting in an accumulation of body fat.

In our studies, 50 per cent of the men and 47 per cent of the women were more than 10 per cent above their optimal weight, using the Metropolitan Life Insurance Company figures as a standard. None of the men and only 13 per cent of the women were under their optimal weight. With an excess of calories, there is a replacement of muscle and other tissues by fat. That excess fat affects longevity unfavorably is well documented for men.

Since excess protein is not stored in the body, regular daily consumption is necessary. Recent work has emphasized that well known supplementary value of proteins. This refers to the ability of one protein to improve the utilization of another when eaten at the same time. Thus the body derives greater nutritional benefit from cereal with milk, or from rice and peas at the same meal, than from these foods eaten separately.

The reasons for recommending a high-protein intake in old age are manifold. However, many older individuals experience difficulty in increasing their consumption of protein foods. Discomfort and refusal are common when a high-protein diet rich in meat, eggs and milk is ordered for an aged individual. This is true of "normal" aged persons as well as for those with anorexia. For these reasons, an amino-acid supplement containing methionine, lysine, and perhaps other essential amino acids may have a useful role in enabling the aged to maintain nitrogen equilibrium. Such a supplement might be in the form of a pill or capsule taken at each meal.

Unfortunately many aged persons cannot afford protein foods and amino-acid supplements. There is a need for cereal products in which the protein is increased both in quantity and quality. This could be attained by a suitable mixture of cereals and perhaps by the addition, in small quantity, of certain key amino acids such as lysine, which is particularly low in the cereal grains. Such a product prepared as a ready-to-eat cereal, bread, or biscuit, at a low price, would find a useful role in the nutrition of the aged and in the prevention of dietary problems.

Hypoproteinemia is a frequent finding in cases of senile pruritis, bed sores, wounds that do not heal, and chronic eczematous dermatoses. The treatment of these conditions with a high-protein intake and the oral administration of amino-acid powders is often successful. The fatigue, edema, anemia and lowered resistance of many old people may be related to a low-protein intake, poor distribution of protein in the day's meals, and impaired protein utilization.

A reduced fat intake with advancing years appears advisable. Our emphasis on the importance of an increased amount of protein in the diet, a mixture of proteins at each meal to insure the efficient utilization of protein, and a decrease in the fat intake, comes largely from our experimental studies during the last few years in the production of atherosclerosis in the monkey. These studies have been under the direction of my colleague, Dr. George Mann.

With the monkey, a primate species like ourselves, we have been successful in producing atherosclerosis by dietary means. Inadequate protein and high fat diets are necessary for its production.

Atherosclerosis has been produced in a number of species over the last fifteen to twenty years. The rabbit was the first such species. In the chick, atherosclerosis occurs naturally and its occurrence has been accelerated by dietary means. In dogs, Kendall gave thiouracil to slow down the thyroid and succeeded in producing atherosclerosis. It has in recent months been established in rats and it was only one or two years ago that we produced it in monkeys.

In all of these species, the key to the development of atherosclerosis seems to be a technique whereby an elevated serum lipid level can be maintained for a sufficiently long period of time. The time varies with the species used. It is short in the rabbit and long in the rat.

The contribution that our laboratory may have made is the discovery that in the primate poor protein in the diet is necessary in addition to increased amounts of fat and cholesterol in order to produce atherosclerosis. By "poor" protein is meant an insufficient amount of the sulfur amino acids, methionine and cystine.

This will no doubt raise the question of whether or not the methyl group of methionine is the material concerned. I think definitely that it is not. Choline, a substance necessary as a methylating agent in the body, must be present in sufficient amounts if atherosclerosis is to occur.

From our experimental studies, it would appear that organic sulfur is the protein component involved in the development of atherosclerosis. In recent studies in man, attention has been drawn to the effect of sudden gain or loss in body weight on the level of blood lipids. If the blood lipid levels are high we believe that weight reduction is a means for lowering them in many individuals. However, as in any aspect of medicine or biology, this can not be 100 per cent effective. In some individuals with high levels of lipids, weight reduction will have no effect, but in most such persons who lose weight, the blood lipid levels will be reduced. On the other hand, in individuals with normal blood lipid levels who suddenly gain weight, it will be found that the concentrations of lipids are likely to increase.

To return to the general subject of nutrition and aging, it may be said in summary that sound nutrition in the elderly differs only slightly from that in the younger adult. The plan should include the following:

1. Fewer calories. Because of the need of fewer calories, activity somewhat above the maintenance level should be encouraged. Such activity will also stimulate the peripheral circulation, strengthen bones, and improve gastrointestinal activity.

2. A smaller proportion of calories contributed by fat and a larger proportion by protein. The protein should be selected to provide good nutritional quality at each meal, but this can also include cereal and vegetable proteins.

3. Dietary modifications necessitated by poor dentures, low income, inadequate cooking facilities, and poor appetite.

The first two of these recommendations would probably improve the health of the young adult and delay the onset of aging.

CONCLUSION

The application of the findings of experimental nutrition to the health of man has great potentialities in many problems of medicine, both therapeutic and preventive. Today this is as important in the health problems of older persons as it was a generation ago in pediatrics, and the anticipated results can be equally important.

DISCUSSION

CHAIRMAN MCGAVACK: Thank you very much Dr. Stare. Dr. Stare's paper is now open for discussion.

DR. DOWD, Massachusetts: As we all know, high potency vitamins are used by the bushel in the oldster. I should like to ask Dr. Stare's opinion as to the need for supplementation of an adequate diet with high-potency vitamins.

DR. O. L. FRIEDMAN, New York City: I should like to ask Dr. Stare if he favors any particular supplemental protein in connection with feeding the aged.

DR. MOUNT, Shelbyville, Kentucky: I should like to ask Dr. Stare about proteins. He has said that we have "good" and "bad" proteins. I should also like to know, in the economic situations in which patients are unable to buy meats, what cereals and what other proteins may be substituted for meat and meat fibers, and whether or not the 19-amino acids would be sufficient replacement.

DR. S. T. HILL, Brooklyn, N. Y.: I should like a comparison between the vegetable and animal proteins in relation to atherosclerosis.

DR. CRAMPTON, New York City: I should like to have Dr. Stare's opinion as to the use of gelatin as an accessory food, in view of the fact that it is low in lysine and tryptophane and possibly some of the other methylating and sulfur elements.

I should like also to know his ideas on the use of phospholipids to keep down lipids, and on the use of iodine throughout the later years of life as a method of thyroid support to supplement direct thyroid medication and to gain the advantages of the use and efficiency of thyroid referred to by two of our speakers.

DR. LEHR, New York City: I want to ask Dr. Stare about two things. He mentioned that choline apparently is not involved in this deficiency of protein. It has been reported this year, both in *Science* and in the *British Medical Journal* that when young and completely healthy rats were given diets deficient only in choline, atherosclerosis developed, with direct degeneration of the heart muscle. Comments were made upon your work and the opinion was expressed that there was a methionine deficiency and a partial choline deficiency.

Secondly, in view of some of the work Dr. Dole and his group at the Rockefeller Institute, who have showed that if you eat more protein you have more appetite, I should like to ask about weight reduction. If you eat protein and get more appetite, how are you going to handle that?

CHAIRMAN MCGAVACK: Dr. Stare.

DR. STARE: The first question was about high vitamin dosages in an adequate diet. I see no reason for anyone, young or old, to take high or low vitamin preparations with an

adequate diet, if they have good absorption and are in good health. On the other hand, there are many individuals eating inadequate diets, particularly among the aged, in whom digestion and elimination are not what they should be. In such cases, I think vitamins are of benefit.

It is better in nutritional medication to give vitamins, minerals, and other nutritional supplements in small quantities and at meal times than to give large doses at longer intervals.

The second question was whether there was any special protein for the aged.

When it comes to a technical discussion of the amino-acid requirements of the aged, we might as well be honest and say that we do not know. Most of our experimental information on amino-acid requirements have come from studies in the rat. In man, our information has come largely from young adults in good health. Conceivably, there are requirements for certain essential amino acids in old age, but no one can give exact information.

In accordance with our present knowledge, proteins that supply the so-called essential amino acids are probably the best for elderly individuals.

Someone raised the question about "good" and "bad" proteins. By "good" proteins is meant proteins that supply the essential amino acids. Those that do not, are not "bad" proteins, but by themselves are insufficient. Two or three "bad" proteins can be properly combined so that they supplement each other and the net result will be an adequate protein mixture.

Certain economic factors come into the picture of diet and nutrition. I thought I brought out in my paper that it is possible to have good diets, furnishing good nutrition and good protein nutrition, without resorting to the more expensive foods. Skimmed milk powder is an excellent protein food and a food reasonable in price. Mixtures of proteins are good. The legumes, peas and beans, are excellent proteins, particularly when they are mixed with cereal proteins.

A question was asked as to the relationship of vegetable and animal proteins to atherosclerosis. To my knowledge, the only study in which protein has been related to atherosclerosis experimentally, and I do not believe this has been shown in man, has been in our work with monkeys, which seemed to show that a lack of the sulfur-bearing amino acids, methionine and cystine, was an important factor.

A question was asked about gelatin. I do not believe that gelatin is an ideal protein supplement. Obviously, it is low in lysine and tryptophane. It is inadequate unless there is also a protein in the diet that supplies sufficient amounts of lysine and tryptophane, or there is some type of medication to provide lysine and tryptophane.

Gelatin is a cheap protein, but by itself is inadequate. In our American way of life, however, no one eats gelatin alone, and if you have gelatin along with milk and cereals it will be satisfactory. In this instance, the over-all protein intake can be increased at low cost.

There was a question with reference to phospholipids. Phospholipids in clinical medicine are, so far as I know, still very much in the experimental stage. We and others have obtained some interesting results, but the studies are not extensive enough for appraisal. Our studies with phospholipids concern their use as a component of fat emulsions we have developed for both intravenous and oral use. Following the administration of such emulsions we frequently have found in both animals and humans lower serum levels of cholesterol, neutral fat, and phospholipids. These emulsions contain several ingredients and we are not sure at this time just which components (phospholipids or others) have this lowering effect, whether it is a real effect, and how transient it may be.

There was a question with reference to protein and the appetite. That subject would be too long to discuss here. However, I do not believe that eating an increased amount of protein will stimulate the appetite. I think it will tend to satisfy the appetite.

PROGRESS AGAINST CANCER WITH RADIOISOTOPES*

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INTRODUCTION

The international availability of radioisotopes produced by nuclear reactors was first announced almost seven years ago at the Fourth meeting of this Congress. It was recognized that this international release would greatly benefit the study and treatment of cancer. Initially available only from the United States, these radioisotopes soon could be procured from Great Britain, Canada, France, and later from Norway. Presently they will be available from reactors in many nations, including Brazil. With modern air transportation, physicians anywhere in the world can be supplied with useful radioisotopes. It is appropriate therefore to evaluate the progress made against cancer with the use of radioisotopes and to look at their potentialities in the future.

The unique properties of radioisotopes fit them for an important role against cancer. Because of their effectiveness as tracer atoms and also as radiation sources, radioisotopes find widespread use in research, diagnosis and therapy (Tables 1–4). Over 47,000 shipments have been made within the United States to about 2,100 institutions, approximately 700 of which are medical. Over 40 per cent of the medical use is in the field of cancer. Over 2,700 shipments have been sent from the United States to 43 other countries, mostly for medical purposes. United States exports are now exceeded in number by those from Harwell in England; other nations, also, are exporting radioisotopes. These figures indicate the widespread acceptance of these relatively new tools.

Because this work is so extensive, it is possible here to survey briefly only major or representative uses in the cancer field. To make a thorough critical survey of all the literature would be a formidable task. Moreover, the world literature on isotopes in cancer is so voluminous that it has been necessary to confine most of the present discussion to work performed in the United States. This is, however, presented only as representative of the great number of studies and applications in other countries.

The use of radioisotopes as sources of a variety of radiations has diversified the field of radiotherapy which originated with the discovery of radium and x-rays. Of more importance, however, is the unique advantage of radioisotopes as sensitive and specific tracer atoms, which makes them powerful tools in the study of life processes. Their greatest long-term contribution may hence be in cancer research.

RESEARCH

The cancer cell itself is the essence of the whole problem and a major part of the cancer research effort is being spent on biochemistry at the cellular level.

* Presented at the Sixth International Cancer Congress, Sao Paulo, Brazil, July 23–29, 1954.

‡ Director, Isotopes Division.

There have been three major approaches to this work: 1) The comparison of metabolic pathways in malignant and normal tissue, in the hope of finding some unique property of the cancer cell which may be used against it. 2) The search for a primary mechanism in the action of chemical carcinogens, which may lead to a way of prevention. 3) The quest for chemotherapeutic agents, which may disclose a means of destroying the cancer while sparing the host. Radioisotopes are playing an important role in all of these approaches.

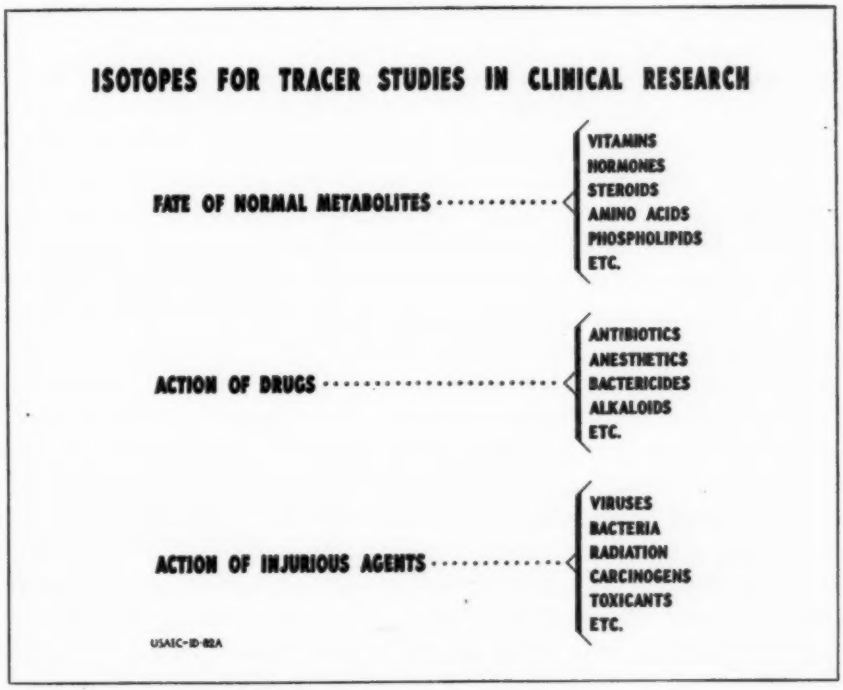
Citric-acid cycle

In the work on metabolic pathways, Weinhouse (1) of Lankenau Hospital Research Institute, for example, is using the tracer technique to shed light on the question of the citric-acid cycle in cancer cells. This cycle, the terminal respiratory system of carbon transport, was formerly thought to be missing in malignant tissue, but with carbon^{14}-labeled carbohydrates and fatty acids, Weinhouse proved that CO_2 is indeed produced and that tumor cells convert the major fuels, glucose and palmitic acid, by an oxidative process to citric acid. All enzymes connected with the citric-acid cycle have been found in various cancers and the cycle is definitely a major metabolic pathway of cancer cells.

Nucleic-acid metabolism

Success against cancer with chemical or physical agents must exploit differences between cancerous and normal tissue. An intense search is consequently being conducted with isotopic tracers to find basic differences. Although no single

TABLE 1



factor has yet been found which distinguishes all cancer cells from all normal ones, potentially useful differences are being brought to light. For example, the substantially faster nucleic-acid synthesis in cancer cells may present a vulnerable metabolic pathway which could be blocked by chemical or biochemical agents.

Nucleic-acid metabolism, because of its fundamental role in life processes, is receiving the greatest share of attention. A recent study by Tyner, Heidelberger and LePage (2) of the University of Wisconsin Medical School, of the incorporation of precursors into ribose and desoxyribose nucleic acids is a typical example of this line of study. They injected glycine labeled with C^{14} into rats with liver tumors. Sacrificing the rats after various intervals, they fractionated the tumors and the livers and then hydrolyzed the nucleic acids of each fraction and separated the nucleotides. The specific activity of C^{14} in each of the isolated mononucleotides was then measured. Knowing how the various activities varied with time, the experimenters could then draw up a flow scheme of the nucleic-acid biosynthesis. As in almost all such metabolism studies, the mechanisms in cancer and normal tissue were found to be essentially the same in kind but not in degree. Significant quantitative differences exist in the details of the intracellular processes.

An interesting side observation was that the tumors had a systemic effect. The normal liver tissue of cancer-bearing rats had a greater proportion of the C^{14} activity in the desoxyribose nucleic-acid nucleotides than did the livers of controls.

Nucleic-acid inhibitors

Knowledge of the differences existing between metabolic behaviors of cancer and normal tissues permits a rational approach to cancer chemotherapy. As C. P. Rhoads (3) of the Sloan-Kettering Institute for Cancer Research describes it, there are three phases or areas in the development of chemical means for control of neoplastic disease. In the first, agents which cause atrophy of specific body tissues induce restraint of neoplasms derived from them. Hormones and radioiodine are examples. In the second, substances are injurious to cells in proportion to the cellular rate of growth. Compounds related to the nitrogen mustards and the antimetabolites to folic acid are presumably in this group. The third phase exploits the metabolic characteristics which distinguish cancer cells from their normal analogs growing at the same rate. In studying all of these agents, radioisotopes are used to trace the biochemical details.

The application of the compound 6-mercapto-purine to man represents perhaps a first step in selective anti-cancer action. This compound and several others which inhibit nucleic-acid synthesis were studied in a program of the Sloan-Kettering Institute, Burroughs Wellcome and Company, Inc., and the Southern Research Institute. In experiments at the Southern Research Institute (4), for example, mice with different types of malignancy were injected with various inhibitors and received isotopically labeled nucleic-acid precursors such as guanine, adenine or formate. The radioactivity later found in the separated metabolic products allowed evaluation of the ability of the different tumors to perform the

various syntheses, and of the relative blocking effects of the drugs on these processes.

L. D. Hamilton (3) of the Sloan-Kettering Institute has extended this type of work to man. He found it possible to follow metabolic activity in ribose and desoxyribose nucleic acids, isolated from leukocytes, for well over two hundred days following a single injection of C^{14}-labeled adenine into a patient with chronic lymphatic leukemia. The results indicate that incorporation of adenine into polynucleotide adenine precedes transformation into guanine in both nucleic acids. Incorporation into ribose nucleic acid is greater and more rapid than into desoxyribose nucleic acid. This indicates a metabolic difference to be exploited in the chemotherapy of leukemia.

An illustration of a tracer study of the chemotherapeutic agent itself is Hamilton's work in collaboration with Elion and Hitchings (3) of the Wellcome Research Laboratories on the fate of 6-mercaptopurine in man. This drug is in active use in the treatment of leukemia, and studies with the sulfur^{35}-labeled compound have demonstrated its rapid metabolism and transformation.

Decreased use of metabolites

Just as some processes are speeded up or intensified in tumors, there is failure to reach normal activity in others. A case in point is the partial failure to convert acetate to other substances. Busch (5) of Yale University School of Medicine found that in various mouse tumors the specific activity of the C^{14}-succinate resulting eight minutes after intravenous injection of C^{14}-labeled acetate was only

TABLE 2

RADIOISOTOPES FOR DIAGNOSIS

ISOTOPE INDICATES FLUID SPACE OR FLOW	BLOOD VOLUME
	BLOOD CIRCULATION TO EXTREMITIES
	RADIOCARDIOGRAPHY
ISOTOPE CONCENTRATED BY SPECIFIC TISSUE	PHYSIOLOGICAL ACTIVITY OF THYROID
	PRE-OPERATIVE LOCALIZATION OF BRAIN TUMOR
	DETERMINATION OF EXTENT OF BRAIN TUMOR

ID-USAEC

1/20 of that in liver, kidney and spleen. Three minutes after injection, 30 to 60 per cent of the total radioactivity was found in glutamate in other tissues but only about 5 per cent was in tumor glutamate.

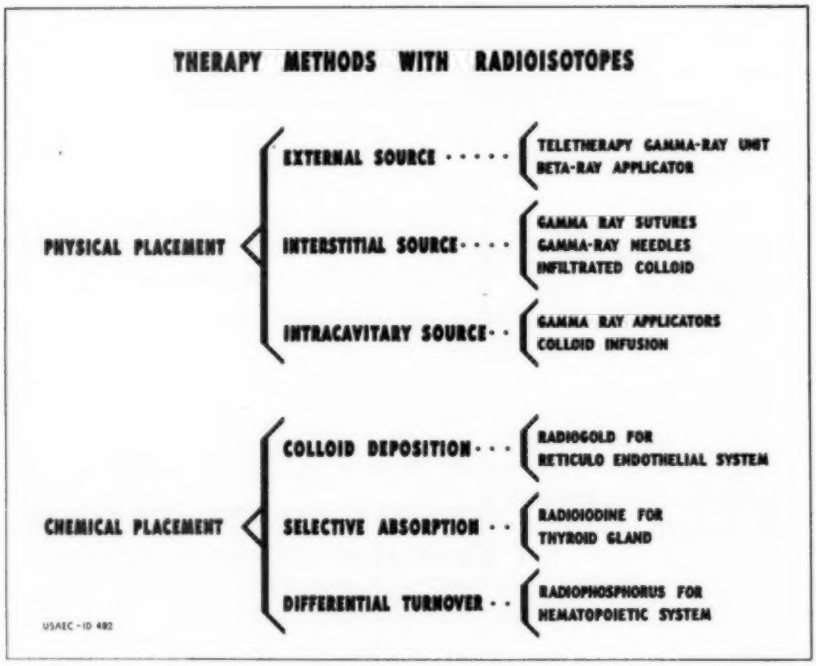
The Biological Laboratory of Southern Research Institute (4) has recently reported another such relative failure in tumor metabolism. The utilization of C^{14}-labeled guanine has been studied in mice and rats bearing a wide spectrum of tumors. In the great majority of cases, the incorporation into tumor was very low compared with that into other tissues. In some cases, this failure was absolute.

Systemic effect of cancer

Of particular interest would be a consistent difference between cancerous and normal patients which would always result in an easily recognizable change in the blood or urine. A simple procedure for detecting such a change might provide the much needed clinical test for cancer.

A recent lead in this direction has been given by Reid, Gilmore and Robbins (6) of Southwestern Medical School, University of Texas. They have studied an as yet unidentified factor which is normally present in blood and which has a regulating action to reduce the speed of transport of high-energy phosphate. This transport is connected with tissue growth and, by comparing the rate of loss of phosphorus^{32}-labeled phosphate from red blood cells of cancer patients and controls, they found that the phosphate transport was higher in the cancer cases

TABLE 3



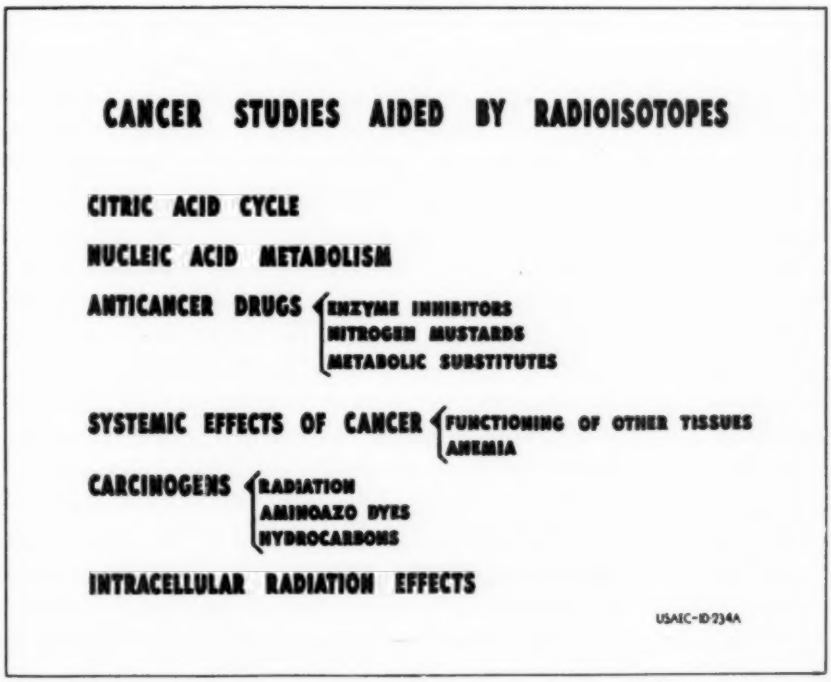
and the amount of the unknown "Q" factor lower. It has been suggested that measurement of the "Q" factor may provide a clinical test for the presence of, or predisposition to cancer.

Many variations between the physiology of normal and tumor-bearing animals have been found. For example, Back and Walaszek (7) of the Department of Pharmacology of the University of Chicago injected C^{14}-labeled colchicine into mice bearing a wide spectrum of tumors. Whereas in normal mice nearly half of the colchicine was found in the spleen, none was found there if a tumor was present in the body. On the other hand, in tumor-bearing mice more of the drug was collected in the intestine. Apparently the intestine reacts to the presence of the tumor with a change in its physiology, inasmuch as other substances such as iodotyrosine and chlorophyll are also accumulated. At the same laboratory, 6 to 8 times as much chlorophyll was found in the gastrointestinal tract of tumorous mice as in that of controls.

In extension of this work to man (8), both patients with extensive cancer and controls free of neoplasm were injected intravenously with C^{14}-labeled colchicine. Within forty-eight hours the cancer patients had excreted only 3 or 4 per cent of the dose as unchanged colchicine in the urine, whereas the controls had excreted from 6 to 15 times as much. This compared favorably with the results obtained with mice, in which the presence of cancer reduced the amount of unchanged colchicine to $\frac{1}{6}$ of normal.

The mechanisms at work in these systemic effects are unknown but tracer studies such as these may supply the key to their understanding.

TABLE 4



Intracellular localization

Because of differences in tumor and normal metabolism, the two types of cells compete for various supplied substances with different degrees of success. Asboe-Hansen (9) of the University Institute of Medical Anatomy in Copenhagen, who is interested in the utilization of sulfur by mast cells in normal and cancerous connective tissue, has shown the results of this type of competition in autoradiographs obtained with sulfur^{35}. After inducing skin tumors in mice, he injected the animals intraperitoneally with the radioisotope and then made tumor tissue preparations two days later. The sulfur was concentrated in mast cells, presumably in sulfuric substances related to the anticoagulative secretions of such cells, and produced intense blackening at their sites in the photographs. Similar exposures to mast cells of normal skin showed little or no blackening.

The effect of such radioactive disintegrations within the cells have been graphically shown by Holt, Sommers and Warren (10) at New England Deaconess Hospital. They injected S^{35}-labeled sulfate into mice with various tumors and then sacrificed them a few hours later. In similar experiments, iron^{55}-labeled ferrous salt and carbon^{14}-alloxan were used. In photomicrographs of the tissues, intranuclear vacuoles were very much in evidence, and in ascitic tumor cells the chromosomes themselves were frequently vacuolated.

Although no substance is likely to be found which will be taken up in this way by all cancer cells to the exclusion of all normal ones, the search for metabolites which approach specificity is an attractive line of endeavor at present. Just as radioiodine is selectively introduced into thyroid tissue, such a metabolite could carry a suicidal dose of radioactivity into the cancer cells.

Carcinogens

The tracer technique is proving valuable in studies of chemical carcinogens, adding to our knowledge of carcinogenesis in general. An outstanding class of these compounds is composed of various polycyclic hydrocarbons, many of which have been studied by Wiest and Heidelberger (11) of the University of Wisconsin. When C^{14}-labeled dibenzanthracene, for example, was applied to mouse skin, it or its metabolite was found chemically bound to protein in nuclear and cytoplasmic fractions of dermis and epidermis. No binding was found in nucleic acids. The same results appeared in studies with the submaxillary gland. Since E. C. Miller (12) found similar binding of azo dyes and acetylaminofluorene in liver and benzpyrene in skin, a common mechanism of tumor genesis involving binding to protein may be present.

An important phase of the work with carcinogens is the identification of the specific substance exerting the primary carcinogenic action. Since this might be either the applied compound or one of its many metabolites, the tracer technique has proved invaluable in the identification. One method of procedure adapted by Heidelberger and his associates (13) has been to apply a labeled carcinogen to mice. A series of chemical separations of the metabolic products then gives considerable information about their chemical nature and allows their synthesis in the laboratory. The identity of a particular metabolite is confirmed if, after mix-

ing with the corresponding synthesized compound, its radioactivity cannot henceforth be separated from the compound. A minimal dose of the carcinogen to a single animal is sufficient in this carrier technique, whereas by former purely chemical methods it was necessary to give enormous doses to large numbers of animals.

Anemia in cancer

The anemia which is frequently associated with cancer could probably have been included in the discussion of systemic effects of cancer but seems sufficiently different to merit a category of its own.

The anemia is understandable in cases of blood loss and nutritional deficiency, but usually the cause is obscure. J. F. Ross of the Robert Dawson Evans Memorial and his associates (14) have been active in attempting to find the mechanism involved and the relation to the neoplastic process. Their paper entitled "The Mechanism of Anemia in Cancer and Related Diseases" is based on these investigations and is on the program of this meeting of the Congress.

Such anemia has usually been attributed simply to a reduced erythrocyte production caused by a partial suppression or replacement of bone marrow by neoplastic tissue. Ross and his coworkers have determined by tracer methods with radioiron that production is, on the contrary, increased in the majority of such anemia cases, particularly in leukemia and malignant lymphoma. Cell survival is at the same time shortened, often to less than half normal, and anemia is the net result.

DIAGNOSIS

Radioisotopes, in their role of tracer atoms, have contributed also to the progress in the field of cancer diagnosis. Several tests or techniques have been developed wherein a selective accumulation of a radioactive element or compound by a malignant tissue reveals its location and extent. Other diagnostic information of frequent importance in cancer, such as blood volume, can also be obtained by the radioactive-tracer method.

Thyroid cancer

The classic example of selective accumulation is, of course, that of iodine in functioning thyroid tissue. The consequent, well known ability of radioiodine to concentrate in the thyroid has made it invaluable as a treatment for hyperthyroidism. In the United States alone last year, over 370 institutions were using the isotope for diagnosis and treatment of thyroid diseases other than cancer. It is unfortunate, indeed, that most thyroid cancer patients cannot be greatly helped with radioiodine.

The primary lesion and its metastases usually fail to exhibit the parent tissue's avidity for iodine. A radioactivity survey after a diagnostic dose of I^{131} frequently fails, therefore, to locate some of the cancerous tissue. Removal of the thyroid gland itself removes its overpowering competition for iodine and allows other functioning thyroid-like tissue to be more easily found. Lack of function

is so commonplace, however, that absence of concentration can give no assurance of absence of thyroid cancer. Nevertheless, definite uptake of radioiodine does disclose functioning metastatic lesions.

Despite its shortcomings, I^{131} remains of considerable value in cancer diagnosis and treatment. More than 250 institutions in the United States use it for these purposes.

Surveying for radioactivity after a diagnostic dose of I^{131}, although often carried out by preference with a hand-carried Geiger counter, has been greatly aided by the newly developed automatic survey or scanning devices. These devices have been made practical by the development of the scintillation counter with its greatly increased gamma-ray sensitivity. They sweep a counter in successive paths across a suspected area and record the resulting pulse rates on a chart to delineate the radioactive sites.

An extension of this type of instrument has recently been built at Donner Laboratory (15) and consists of ten scintillation counters which travel side by side. Each counter surveys a narrow path and controls the brightness of its corresponding lamp in a bank of ten neon lamps. These lamps move past a camera in synchronism with the counters and expose the photographic film in a pattern which duplicates the pattern of radioactivity. A series of such scintillation surveys can be assembled to produce a wholebody diagram.

Brain tumors

The gamma radiation of I^{131} has also been found useful for locating tumors through the intact skull. Various substances have been tagged with this isotope for biochemical concentration in the tumors, after which a survey with a directional counter indicates the position of the growth. Brain tissue is normally protected by the so-called blood-brain barrier. This barrier, however, is impaired in lesions and substances may temporarily accumulate in the extracellular spaces of the tumor. Diiodofluorescein has been much used as the carrier of I^{131} to brain tumors, but iodinated human serum albumin is now the agent of choice.

Accurate outlining of radioactive areas is considerably more difficult in the brain than in the thyroid. Because of the increased amount of surrounding structure, a considerable degree of gamma-ray scattering occurs, which blurs the outlines. Also, concentrations of radioactivity ranging only from 1.6 to 29 relative to surrounding tissue have been reported, whereas a relative concentration of about 10,000 is characteristic of the thyroid. With this low relative intensity, the scattered and background radiations assume added prominence.

These difficulties have been avoided by H. C. Allen of the Veterans Administration Hospital of Houston, Texas, and his associates (16). In their technique they employ a highly directional scintillation counter and a recording system which accepts only those pulses which correspond in size to the 364-kev primary gamma ray of I^{131}. Only I^{131} concentrations are depicted on the resulting chart, because scattered radiation is degraded in energy from the primary value and background radiation is either too high or too low in energy.

Brownell and Sweet (17) of Massachusetts General Hospital have developed

another scanning device for brain tumors. It employs two opposed scintillation counters, one to scan each side of the head, and is designed to count only coincidences between gamma rays. It can, therefore, avoid the scattered and background radiation by detecting only the presence of positron-emitting sources such as concentrations of copper^{64} or arsenic^{74}. The decay of positrons immediately after emission is attended by the production of two oppositely directed gamma rays, and thus coincident pulses are registered by the counters when they are aligned with a tumor-concentrated region of positron activity.

Other uses of scanners

The success in obtaining scintillation surveys of brain tumors and functioning thyroid cancer has stimulated the use of the technique in other diagnoses. Yuhl, Stirrett and Cassen (18) of the Veterans Administration Center, Los Angeles, and the School of Medicine of the University of California at Los Angeles, have applied the technique with radioiodine-labeled human serum albumin in producing outlines of liver tumors. They have also injected this material into the spinal subarachnoid space for a similar purpose, and have used various I^{131}-labeled compounds and the scanning device to outline the gallbladder.

Breast cancer

Because of the rapid turnover of phosphorus in areas of accelerated metabolism, there is a temporary 8- to 100-fold concentration of P^{32} in such areas after a diagnostic dose. When this concentration occurs in a relatively superficial cancer, as in the breast for example, the fraction of the applied dose taken up by the cancer can be determined with a sensitive radiation counter. The growth or regression of the lesion, as influenced by therapy, may thus be assayed from time to time.

Inasmuch as benign tumors and other growing tissue also concentrate the isotope, malignancy cannot definitely be distinguished. In some hands, however, as early reported by Low-Beer (19), the method is useful even in original diagnosis.

The beta particles from P^{32} cannot penetrate to the counter through more than 7 or 8 mm. of tissue. To extend the method to cancer at greater depth, Nathanson, Baker and Selverstone (20) of the Huntington Memorial and Massachusetts General Hospitals have used potassium^{42} instead. This also has a rapid turnover in growing tissue. Potassium^{42} emits a 1.5-Mev gamma ray which is easily detected with a lead-collimated scintillation counter. Doses of 200 to 500 microcuries were found effective and the usual time for optimum concentration to be reached was about fifteen minutes after administration.

THERAPY

Radioisotopes have contributed substantially to cancer therapy during recent years. Actual therapeutic results cannot be discussed in terms of 5-year or 10-year cures, because there has hardly been time for comparative long-term statistical results with enough patients. The results, by and large, have not been startling, or as good as once hoped. Nevertheless, radioisotopes have been a useful adjunct

to other therapeutic methods. The additional years of useful life afforded to the patients helped by isotope therapy amount to an impressive total. The palliative benefit also has been considerable and, from the long-term viewpoint, both successes and failures have already added invaluably to our knowledge of cancer and what can and cannot be done to treat it.

The important consideration in the therapeutic use of a given radioisotope is the internal or external placement of the radiation source where it will have the greatest effect on the cancer and the least effect on normal tissue. For internal use, two modes of placement are available, biochemical and physical. External use includes surface application, as by plaques or applicators, and beam irradiation by teletherapy units.

Biochemical placement

In biochemical placement, a difference in behavior of cancerous and normal tissue is relied on. This difference may be inherited from a host organ, as in the case of thyroid cancer; it may be the increased need of an actively growing tissue or an unusual need of an abnormal growth; or it may be the letting down of a normal defense against entrance of a foreign substance.

To serve effectively in biochemical placement, a radioisotope must have certain characteristics. It must be available with high enough specific activity to be effective in small quantity, especially if chemically toxic to the body. It must have an appropriate half-life, both radioactive and biologic. The isotope or the substance into which it is to be incorporated must have a tendency to concentrate in or near the tissue to be destroyed. The localization must be established in a reasonably short time after administration, so that a minimum effect is produced on healthy tissues. Finally, the radiations must be effective only within a very short range, since it is localization of the effect rather than of the isotope which is basic in the technique.

At present, I^{131} (8-day half-life) and P^{32} (14.3-day half-life) are the only isotopes which have met these specifications well enough for extensive use. Others, however, have sufficient affinity for certain tissues or enough of the foregoing qualifications to fit them for specific uses. Much research is being directed toward adding to the list.

Thyroid cancer. Although the ability of I^{131} to destroy thyroid tissue has been amply demonstrated, the difficulty in treating thyroid cancer lies in the failure of the cancer to perform like normal thyroid tissue.

As Andrews (21) of Oak Ridge Institute of Nuclear Studies has said, "In general it appears that not more than 10 or 15 per cent of patients with thyroid tumor can be greatly helped with radioiodine at present. These figures, which are somewhat disappointing, are offset by the fact that a great deal of new and valuable information about thyroid carcinoma has been forthcoming and there are further possibilities of improving therapeutic results."

There are two schools of thought regarding the stimulation of iodine collection by thyroid cancers. Both are based on the specific action of thyrotropic hormone, one relying on the hormone as secreted by the pituitary gland, and the other on administered doses.

In the program established by Rawson and his associates (22) at Memorial Center for Cancer and Allied Diseases, for example, complete removal of the thyroid and of any accessible extensions and metastatic lesions is first accomplished. This is followed by I^{131} tracer studies every few weeks, to determine if any of the remaining metastases have been stimulated to function by the resulting hypothyroid state. A course of daily thiouracil is started within three to six months, in order to augment the hypothyroid state, and is interrupted every few weeks for uptake study.

If, during any of the tests, less than 40 per cent of the tracer iodine is excreted in four days, the patient is considered ready for a therapeutic dose. Another tracer study is made before therapy, to determine the fraction of the radiation which will be delivered to other tissues, including the blood-forming system. A maximum dose is then calculated which will not seriously harm the patient.

By following these rather rigid criteria, this group has demonstrated that a large percentage of cancers of the thyroid can be made to assume certain functions of normal thyroid tissue, and that certain cancers of the thyroid can be at least partially destroyed with radioiodine.

In contrast to this method, the program of Starr and his co-workers (23) at the University of Southern California School of Medicine is based on the belief that slow, chronic stimulation by the pituitary induces growth and proliferation of the metastases, rather than merely increased function. They seek to suppress this action. One week after removal of the thyroid and primary lesion the patient is given a diagnostic dose of I^{131} and if less than 70 per cent is excreted in three days, he is considered ready for a therapeutic dose. If he is not, they deliberately suppress the pituitary action by maintaining a euthyroid state with daily thyroxine or desiccated thyroid. A short, intensive course of daily thyrotropic hormone is then given to stimulate iodine collection, and a tracer study is made. If more than 70 per cent of the radioiodine is again excreted in three days, the euthyroid state is maintained for four to six months to see whether sensitivity to the stimulating hormone will increase. Another tracer study is then made and repeated at 4- to 6-month intervals. A therapeutic dose of 100 millicuries of I^{131} is administered whenever a tracer study indicates that the patient is ready. Monthly uptake studies are made thereafter to determine the effectiveness of the therapy.

It is too early in radioisotope therapy to evaluate properly either of these modes of treatment, or even to compare their results. It seems that in half the cases thyroidectomy alone will stimulate metastases to significant function within six months and that thiouracil treatment will do the same. Only about one third of the few patients maintained, so far, in the euthyroid state have had their iodine collection increased sufficiently for a therapeutic dose. There is advantage, however, in avoiding the unpleasantness of profound myxedema over long periods.

Polycythemia vera. Biochemical placement of radiophosphorus was first used in the treatment of polycythemia vera in 1938. Since its increase in availability as a reactor-produced isotope, P^{32} has become the treatment of choice in this neoplastic-like blood condition. Lawrence, Berlin and Huff (24) of Donner Laboratory, University of California, consider the advent of radiophosphorus to have

given the polycythemia vera patient an almost normal life expectancy, practically twice that obtained with drugs, blood-letting, and x-ray therapy, and even better than that with insulin in diabetes, or with liver in pernicious anemia. The expectancy would be still greater if it were not for the deaths due to the leukemia which is present in about 20 per cent of the polycythemia vera cases. In reporting on 200 cases treated with P^{32}, unexplained red cell counts over 7,000,000 or high counts plus an enlarged spleen were considered diagnostic of the disease. A reduction in the red cell count to 5.5 million was regarded as a remission. On this basis, they report a 94 per cent remission. Of the principal symptoms, headache was improved in 92 per cent of the cases; other symptoms such as dyspnea, eye and stomach troubles, and chest pains were improved in 74 to 85 per cent.

Physical placement

Radioisotopes are physically placed in or near the cancer itself when the site of malignancy is accessible or can be reached with a minimum of surgery.

Such placement is accomplished by intracavitary or interstitial injection or by interstitial implants. In the injection techniques a colloidal form of the radioisotope is usually employed in order to obtain insoluble, non-metabolizing sources of radiation. If the radioelement or the compound containing it is insoluble in body fluids and is not metabolized, it tends to remain where it is placed. Implantation techniques involve the use of wires, needles, or grains in extension of the well known radium and radon techniques.

Intracavitary injection. A good example of the palliative power of radioisotopes is the ability of intrapleural or intraperitoneal injections of radiogold colloid (2.7-day Au^{198}) to inhibit serous effusions. Often the pain from the secondary effects of carcinoma, and the disturbance due to the pressure on adjacent organs, constitute the chief if not the entire awareness the patient has of his disease. Reduction or prevention of the fluid formation can make his existence tolerable or even pleasant while treatment of his disease is attempted.

There seems to be no special affinity between the tumorous tissue and the gold. The colloid is rapidly removed from the fluid to the cavity lining after instillation, mostly or entirely by the action of phagocytes. A small but appreciable quantity escapes from the serosal cavity through the lymphatic channels to the blood and thence to liver, spleen and marrow. Hahn and Goldie (25) found that the 0.2 per cent or less which appears in the blood within the first ten days is entirely in the plasma, protein-bound to the alpha and beta globulins.

Reports by those using Au^{198} for effusions indicate that approximately half of the patients treated obtain relief from their symptoms. The general opinion is that radiogold is best suited to cases in which the cancer is growing slowly and in which the accumulation of fluid is the most important symptom.

Elkins (26) has reported that he and others at Iowa State University use the colloid as a prophylactic measure in the operating room when the contents of a cystic carcinoma of the ovary are spilled into the peritoneal cavity.

Radioactive gold and silver-coated radioactive gold colloids have been in-

stilled into the lung and are found to drain through the lymphatic system, thus following the pathway of metastatic dispersal. As yet, insufficient work has been performed with humans to allow routine application. However, as Hahn, Hilliard and Carothers (27) of Meharry Medical College suggest, in cases in which it is certain that a lobe is to be removed, the instillation into it, two weeks before operation, of sufficient radiocolloid to treat the affected lymph nodes may reduce metastatic spread and extend the life-span of the patient. Radiation necrosis of the lung tissue itself can be tolerated, they suggest, inasmuch as the lung would be serving merely as a temporary transfer source to the lymphatics.

Lanthanum^{140} (pure beta emitter, half-life 40 hours) has also been used to reduce serous effusions. Hart and Greenberg (28) of Montefiore Hospital, New York, injected the chloride intrapleurally and found they could remove the lanthanum completely when they so desired, by intrapleural instillation of ethylenediamine tetra-acetic acid. Greater efficiency is allowed when a removal of this kind can be carried out, because higher doses may be administered with assurance that the exposure can be terminated.

Phosphorus^{32} in the form of colloidal chromic phosphate, has possible advantages over gold colloid for intracavitary and interstitial injection, and has been supplanting it in some hospitals.

Yttrium^{90} (2.6-day half-life), also a pure beta emitter, is of interest as another agent for radiocolloid applications. The chloride is reported (29) to become colloidal when injected into body fluids or tissues, and the radioisotope itself can be repeatedly milked from its long-lived parent, strontium^{90} (25-year half-life) in a separating column. Additional research is required, however, to determine its biochemical behavior before it can come into common use.

Interstitial injection. Interstitial injection of radioactive colloid provides a useful mode of treatment of many types of accessible but inoperable malignant masses. Tumors which, because of proximity to delicate organs, lack of definite boundary, or the precarious condition of the patient, are not suitable for surgical removal are often reduced by the injections. The chief limiting factor in this use has been the inability of friable and softer types of cancerous tissue to retain the colloid. The main advantage of this mode of treatment, when it is applicable, is that lesions may be treated with large doses of radiation which could not be administered with external x-rays.

The object is to disperse throughout the cancerous mass a practically continuous source of lethal radiation. To function properly and efficiently, such a source should emit very short-ranged radiation for localized effect, should have a relatively short half-life, and should be insoluble in body fluids.

Colloidal radiogold meets these requirements satisfactorily. Its beta particles have a range of only 3 or 4 mm. in tissue, which confines their lethal activity to the site. Its 0.4-Mev gamma ray, however, produces 5 to 10 per cent of the total ionization in tissue and, since it can reach other organs, constitutes one of the disadvantages of the material.

Only 5 to 10 per cent of *prostate cancer* cases are found while still in the stage in which excision of the prostate and capsule can result in a cure. In about half

the cases, the tumor has invaded the surroundings, and it is in this class that interstitial injection of radiogold colloid has been used with good effect. In the remaining cases, spread has occurred to distant areas, usually bone or lungs, and insufficient gold is carried to the sites by the blood stream to have a significant effect.

Encouraging results have been obtained when the colloid has been used before the occurrence of metastasis. Elkins and Flocks (30) of University of Iowa Medical School, in reporting on the first 129 cases, state that the most striking thing to be noted is the rapid regression in the size of the prostate. In seven to ten days a large nodular prostate can shrink until barely palpable. Since Flock's original use of the colloid in March 1951, over 98 per cent of their patients have experienced this clinical improvement. Seventy-four of the original 100 were still alive over two years later, 35 of these being without clinical evidence of carcinoma. Ten others, also free from cancer, died from other causes.

Both radical surgery and x-irradiation, when they fail in cases of *cancer of the cervix*, do so primarily because of residual neoplasm in the original lymph nodes and lateral parametrial areas. It has been demonstrated that radiogold colloid can reach the lymph nodes for localized destruction after injection near the tumor mass. Routine use of the isotope for treatment of both the primary and metastatic lesions awaits solution of technical difficulties. These are chiefly the obtainment of an even dispersion throughout the tumor and the prevention of a hazardous amount of radiation to the therapist. Special equipment and techniques are being developed, however, to overcome these obstacles.

Soule (31) of Washington University Medical Center has described the evaluation made there of radiogold colloid as a therapeutic agent for cervical carcinoma. From direct measurement at the time of subsequent surgery and measurement of the radioactivity of excised tissues, it was found that 50 to 75 mc. injected into each parametrium delivers on the order of 75,000 rep at the injection site, primarily by beta radiation. The obturator and hypogastric groups of lymph nodes receive between 20,000 and 75,000 rep. Definite deposits of the gold were found in the nodes, associated with cellular destruction and accompanying fibrosis. Definite radiation effects were noted in parametrial areas and, at operation, some of the out-lying irremovable tissues laterally on the pelvic wall showed infiltration with gold.

Implantation. The third mode of physical placement of radioisotopes is exemplified by the interstitial implantation of radiocobalt as a substitute for radium. Although both have about the same effective gamma-ray energy, cobalt has a number of advantages. As was early pointed out by Myers (32) of Ohio State University, these include the possibility of greater variety in shapes, types, and dosage distribution, greater ease of handling, homogeneity of radiation, ease of shielding out beta radiation, absence of gaseous radioactive daughters, desirable metallurgical properties, reduced toxicity, and greatly reduced cost. The chief disadvantage is the shorter half-life of radiocobalt, which necessitates frequent correction of activity.

The 0.31-Mev beta rays of Co^{60} are easily filtered out by a thin metal sheath and various types of sheaths have been used in producing needles for implanta-

tion. Meschan and his associates at the University of Arkansas School of Medicine (33) found that the 1.65-mm. hyperchrome steel tubing used for hypodermic needles is suitable for the purpose. They crush one end flat and drill it as an eyelet. The radioactive wire is then inserted and the open end is sealed with silver solder.

The group at Ohio State University have also used thin stainless steel tubing as a sheath. This group initiated the use of short lengths of the cobalt wire spaced in thin nylon tubing which can be sewn into the tissues (34). A configuration calculated to produce the desired radiation pattern is thus simply obtained and the entire implant can be easily withdrawn.

Radioactive tantalum wire encased in platinum has come into favor in some hospitals in England. Sinclair and others (35) at the Royal Cancer Hospital in London have used it in a large variety of cancers. They find that it has certain advantages over cobalt which offset the inconvenience of a shorter half-life (Ta^{182}, 117 days; Co^{60}, 5.3 years).

Interstitial implants also take the form of short lengths of radioactive gold wire encased in nonactive gold tubing. These are comparable to the well known radon seeds and, because of the short half-life of radiogold, can be left in the tissues permanently. The gold seeds have entirely supplanted radon at Ohio State University (36), where it has been found that the encased wire can be conveniently cut in the operating room to provide the desired amount of radioactivity. The simple act of cutting seals the ends sufficiently against beta-ray leakage. As with cobalt, nylon tubing is frequently used to sew the gold wires into the tissues.

Topical application

As external sources of radiation, isotopes are being applied in various ways to skin cancers and other malignant lesions on or near the surface of the body. By the use of pure beta-ray emitters an intense effect is produced within the first few millimeters, with no hazard to deeper normal tissue. Strontium^{90} is regularly mounted as such a source in devices which can be conveniently handled and applied to ophthalmic lesions. The use of a Sr^{90} applicator was pioneered in the United States by Friedell and co-workers (37) at Western Reserve University. This group had felt the need of a beta-ray source to supplant the radon bulbs it had been using. By the choice of strontium they gained a half-life of 25 years instead of 3.8 days, simplicity of fabrication, and freedom from gamma radiation.

Solutions of radioactive compounds, such as P^{32}-active sodium phosphate, may be absorbed in appropriately shaped pads and placed in contact with cancerous areas of the skin as was done seven years ago by Low-Beer (38). K. E. Scheer (39) has shown how finely powdered radiocobalt can be intimately mixed with plastic materials which can then be molded to fit a particular area. These surface methods have been used by some clinicians with considerable success.

Teletherapy

The relatively new teletherapy units have some advantages over x-ray machines in compactness, maneuverability, and cost. The units at present in opera-

tion employ Co^{60}, the only high-energy gamma-ray emitter which has been obtainable in sufficient quantity and specific activity.

In the summer of 1951, two 1,000-curie cobalt sources were produced at Chalk River, Canada and were mounted in teletherapy units at the University Hospital in Saskatoon and Victoria Hospital in London, Ontario. H. E. Johns (40) of the University of Saskatchewan designed the first of these and compared the depth-dose from Co^{60} with that of a 3-Mev x-ray machine.

Ten or more teletherapy units are now in operation in the United States and 20 or 30 more are awaiting the high-activity cobalt being irradiated in high-neutron-flux reactors.

A need has been felt for sources of lower energy than radiocobalt because of the reduced amount of shielding they would require in the units as well as in the treatment room. The use of 37-year cesium^{137} has been particularly recommended by Brucer (41) of the Oak Ridge Institute of Nuclear Studies. The 660-kev gamma rays of cesium are easily shielded and Brucer showed that a 500-curie source would be adequately shielded at the center of a 33-cm. lead sphere. Only a few more centimeters would suffice for 2,000 curies.

The first kilocurie source of Cs^{137} has just recently been announced by Oak Ridge National Laboratory and will be mounted in a unit for cancer therapy at the Medical Division of the Institute of Nuclear Studies. The separated fission product was compressed into a small pellet having 1,540 curies of activity.

SUMMARY

In conclusion: 1) The greatest value of radioisotopes to date in the cancer field has been in research on biochemical details of cancer cells and the mechanisms of agents which affect these cells. 2) The potentialities appear very promising for diagnostic tests which depend either on a selective uptake of radiomaterials by cancer tissue or by a systemic change in metabolism of a radio compound due to the presence of cancer. However, actual diagnostic applications are still rather limited. 3) In therapy, much hope has been placed on obtaining selective biochemical concentration of radiomaterial by cancer tissue, but here also the clinical applications are limited. Greatest progress has been made in developing new ways to obtain advantageous physical placement of radiomaterials by interstitial injection, instillation into cavities, or implantation. Gamma-ray-beam devices have also been developed which produce results similar to those obtained with million-volt-range x-ray equipment, but which have certain advantages in obtaining desirable radiation dosage patterns. 4) Thus, research teams find radioisotopes invaluable and indispensable tools and, although clinical teams do not find them indispensable, they are often considered to be advantageous additions to other modalities.

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THE PRACTICE OF GERIATRICS*

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It is a statistical fact that as a nation we are getting older. The increase in population is matched by a disproportionate increase in older people. Now, old age is to be reached and enjoyed by the majority instead of the minority. We are faced with the medical paradox that any progress made in the control of chronic diseases such as tuberculosis, diabetes, hypertension or heart disease will result in a further increase in the numbers of the aged and their problems, especially those due to chronic invalidism.

The writer realized early in his practice that a large percentage of it concerned patients over 60 years of age, and that he apparently favored working with this group. This discovery was followed by a deliberate effort to encourage the trend, so that now over 90 per cent of the practice concerns patients over 60 years old. In preparation for this type of practice, the writer endeavored to study closely those diseases prevalent among the aged. He attended courses and clinics offering this training, read texts and journals devoted to the diseases and problems of the aged and the chronically ill, became a member of the American Gerontological Society and the American Geriatrics Society, and became affiliated with hospitals and homes for the aged and the chronically ill. Whenever time permitted he participated in community affairs concerned with aging.

The following observations seem worthy of note in the practice of geriatrics:

The office should be easily accessible, preferably on the ground floor, and have an ample parking area. It should be well lighted, ventilated and soundproofed. Waiting is to be avoided and the staff must be patient and sympathetic.

The records employed vary, depending upon the personnel available and preference by the physician. The following have been found useful:

a. The Cornell Medical Index; this is not to be used in lieu of a careful history taken by the physician, but rather to supplement it (1). It is filled out by the patient at his leisure at home, where he will have ample time to review his past and note his symptoms. To this questionnaire may be added a supplement to suit the fancy of the physician who may be interested in a particular phase of the history. On subsequent visits this will be reviewed by the physician and further information will be added to that obtained previously. This is especially important, since the history is usually long and the memory often short. It is also a medium by which a very loquacious or rambling person may be controlled.

b. Physical examination forms are of many types and as detailed as the

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physician desires, or he may have one printed to suit his needs. However, the important thing is the thoroughness of the examination and the recording of all findings at the time of the examination so that later variations will be noted.

c. A record of daily activities is probably one of the most important reports submitted by the patient. This also is filled out by the patient at home and should give a reliable account of his activities, physical capacity, recreation and social behavior. A comparison of this record with the history previously obtained may show some discrepancies.

d. The patient's notes, which often are brought in at each visit, may reveal many traits, such as a tendency to hypochondriasis, poor memory, tremors or unsteadiness, and at times aberrations in thought. Comparison of notes written later may show changes.

e. Reports and correspondence from physicians, hospitals and laboratories are important and at times difficult to obtain, especially when a patient has a voluminous history and has frequently changed residence or physicians. For this reason, continuity of care may be difficult to obtain. Crampton (2) has repeatedly advocated the use of a 'life health record' or 'health passport' into which the various physicians would make entries of all the medical and surgical illnesses for which the patient had received treatment. This record would be carried by the patient and thus be readily available to succeeding physicians.

f. Photographs and recordings are of value in selected cases, to show physical changes and alterations in personality.

The interview should be in an atmosphere of complete relaxation, avoiding haste and abruptness. It is to be an occasion for mental catharsis by the patient. It is important to evaluate the patient's memory, alertness, concentration and educational background. The history may be long and confused, often full of inaccuracies and omissions of important events in medical and surgical experiences. At times one may detect a deliberate coloring by exaggeration, distortion of facts, possibly evidence of family dissension, resentment, intimidation or dependency upon others. One must evaluate the effect of environment, economic and social background, and all the work experience. Frequently a patient's description of a symptom may be difficult to evaluate, and only time and patience will make it possible to understand what he is trying to convey.

The physical examination begins when the patient is first seen; such things as the general appearance, gait, alertness, mannerisms, neatness of dress, need of assistance in ambulation, use of mechanical aids, defects in speech, sight and hearing should be noted. It is to be a fact-finding examination, noting normal and abnormal findings for the *age* of the patient. Many old people are reluctant to be examined thoroughly, often requesting that the examination be limited to that part of the body which troubles them at the time. However, with patience and tact, they eventually will relent and permit a more complete study, including rectal, vaginal, sigmoidoscopical, laryngeal and ophthalmoscopic examinations, as required. These should be carried out within the succeeding weeks or months, as should also all pertinent laboratory and x-ray work. This may mean

referral to other physicians or laboratories, and great care should be taken to explain the need for such referrals in order that the cooperation of the patient is assured. The need for a dental survey is to be emphasized. Care should be taken to avoid undue fatigue of the elderly, since some of the diagnostic procedures may tax their physical endurance. Photographs of the patient may be taken, focusing on that part of the anatomy or the lesion specially concerned.

The evaluation of the patient should include all of the body systems, and there are usually multiple diagnoses. The mental status, and the physical capacity of the patient are to be considered, as outlined by Zeman (3). This will determine the physical limitations to be imposed upon the patient. Fear and apprehension are to be avoided.

The course of treatment and schedule of visits should be outlined to the patient and family. Emphasis is to be placed upon the preventive aspects of geriatrics, such as the correction of overnutrition, or undernutrition, the performance of elective surgical procedures such as herniorrhaphy, repair of rectocele and cystocele, prostatectomy, cholecystectomy, biopsy or excision of skin or mucosal lesions, and the obtaining of proper dentures, orthopedic appliances, hearing aids or lenses. It is better to spend a few minutes in explaining organ physiology or function, than it is to hasten the patient out of the office with a prescription. Reading matter in the form of pamphlets may be given to patients who may profit by them.

In the care of the aged, it is best to proceed slowly and cautiously. Overtreatment is especially to be avoided. The effects of drugs are noted carefully, and it is good practice to ask what drugs the patient has taken in the past and what have been the reactions. The same caution applies to a new dietary regimen, since intolerance to certain foods is common. Advice on the preparation of food is important, since there may be limitations imposed by poor dentition, decreased secretion by the salivary glands, achlorhydria, gallbladder disease, or previous operation upon the gastrointestinal tract. Into consideration must be taken the patient's financial status, since his purchases may be limited to the cheaper foodstuffs, involving a disproportionate amount of starches, eventually leading to protein depletion and vitamin deficiencies. Food fads are discouraged for the same reason. Of special nutritive value are the "baby foods" and the "junior foods" which are available in great variety to satisfy all tastes and varied nutritive requirements. In addition, they have low salt and low fat content. These foods are of great convenience to those who are alone or homebound, or perhaps physically incapacitated and therefore unable to prepare elaborate meals. Some of the "baby foods" may be further diluted with water, milk or bouillon and thus used for tubal alimentation.

When not contraindicated, appetite may be stimulated by a few ounces of wine or brandy, which are preferable to cocktails or whisky. This will provide extra calories and a feeling of well being.

The physician may discern misconception concerning some disease on the part of the patient. A little time devoted to a discussion of the illness often will eliminate confusion and undue apprehension, and may assure the patient's

cooperation. This is especially true in discussing hypertension; and the taking of the blood pressure at each visit will focus the patient's attention to it.

Elderly patients who are ill with a chronic disease require medications for long periods of time. For these people the cost of drugs and medical care is a real burden, and therefore the physician should request only essential laboratory work, and prescribe only drugs of proven merit. Hospitalization is to be advised with discretion, since most hospital insurance plans do not give coverage to the aged and the chronically ill.

The impact of enforced retirement, the loss of dear ones and friends, the progressive loss of physical ability due to the aging process and the onset of crippling disease, all very often lead to periods of depression and hopelessness. It requires the greatest tact and patience on the part of the physician to allay such fears and direct interest along wholesome lines. The geriatrician should be well versed in techniques of physical and social rehabilitation. The changes which are part of the normal aging process should be explained to the patient in order that he may better understand the limitations imposed upon him.

Surgery in the aged (4, 5) is becoming increasingly favorable due to improved anesthesia, better surgical technique, the use of antibiotics, and attention to subclinical nutritional deficiencies and supportive therapy. Rehabilitative measures are started soon after an operative procedure or an illness. Since accidents are the third cause of death, it behooves the physician to alert patients regarding their proneness to accidents, especially those with poor visual acuity, defective hearing, poor gait, or vertigo, and those who use canes, crutches, or other mechanical devices. Such things as waxed floors, scatter rugs, stairs or poor lighting contribute to accidents.

Upon investigating the family's attitude toward the aged member of the household, one may discern a tendency toward hopelessness and laissez faire, or lack of cooperation and understanding, and occasionally actual hostility. Patients who have a devoted family seldom seek entrance into a home for the aged, especially when custodial care is the only need (6). With intelligent cooperation, the relatives may be taught simple nursing procedures, administration of medications including parenteral therapy, the changing of dressings, and simple laboratory tests. These may be supplemented by the services of the neighborhood visiting nurse. If, in addition, there be frequent visits by relatives and friends, religious guidance, and some form of occupational interest, the patient's life becomes well rounded out. He becomes contented and feels loved and wanted, and therefore still a useful member of society. Every measure should be taken to keep the oldster in his home and community, and to admit him to an institution only as a last resort, even though the better homes for the aged do provide many comforts and services.

Retirement should not be determined arbitrarily by the chronologic age, but rather by the person's physiologic age, which varies greatly among individuals. Retirement should be achieved gradually, possibly by working a few hours a day, or perhaps changing to a lower-level occupation requiring less exertion. Simultaneously, interest is to be cultivated for some wholesome hobby or ac-

tivity which will engross him in his later years. Only by such preparation for the later years will the frustration and inactivity which we now find among the aged be reduced. Medical science has increased life expectancy, but society has decreased the span of occupational usefulness. Geriatric rehabilitation includes not only medical, but also social and economic rehabilitation.

The geriatrician can render valuable services to the community (6) as a consultant on matters relating to the aged and the chronically ill, such as facilities for their care and housing, home-care programs, housekeeper services, rehabilitation, organization of courses for the chronically ill and the care of the aged, foster homes for the aged, recreation and adult education programs. Above all, he should work with other groups interested in these matters, be they in medical, social, economic or other fields (7).

Preparation for this type of practice would be facilitated by placing greater emphasis upon the aging process and chronic diseases in the training of the physician. Also, geriatrics divisions and clinics should be established in the larger hospitals and homes for the aged. These would serve as a training medium for interested physicians (8).

The practice of geriatrics is difficult and time-consuming. However, there is great satisfaction in the appreciation shown by patients who are grateful for the interest taken in their welfare.

SUMMARY

An outline is presented of the practical aspects in the practice of geriatrics. Observations are made of the problems usually encountered, including the social and economic ones. The relation of the geriatrician to the community is discussed. The need for establishment of geriatrics divisions and clinics in the larger hospitals and homes for the aged is stressed.

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DIAGNOSTIC SCREENING PROCEDURES FOR THE OFFICE

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A reasonably complete medical work-up can be a satisfaction to both patient and physician. When carried out early in the doctor-patient relationship, it is often an economy that avoids a series of brief, mutually unsatisfying office visits. Systematic methods of examination used in large clinics have been eminently successful. Likewise in the office, efficiency improves with a previously planned methodology adapted to the circumstances.

How many bits of information can be obtained in two thirty-minute consultations several days apart? An answer involves skill in setting the stage—securing a proper attitude, then selected screening procedures. These deserve organized study in the future. The clinician's task is to discard nonessentials and obviously false leads while pursuing the possibly important. Limitations of time can be countered only by intensifying the search for information and this generally means programming or developing routine procedures. Learned actions come easily and rapidly; intellectual decisions, slowly and with difficulty. Each choice is necessarily a compromise, for both generalizations and specializations are subject to the criticism of omissions. Each attitude or act of the physician, each word he utters has an effect—again emphasizing the need for a planned protocol. Although this requires a dominance in relationship to the patient, the demand is for friendly cooperation. Fear, disbelief and hostility have no place, and blind subservience doesn't suffice.

Telling his story is usually uppermost in a patient's mind and most of the first visit must be devoted to translating and counteracting the vagaries of memory and interpersonal communication. A set of weighted values is needed for reconstructing the sequence of events or feelings described, so a personality appraisal is inevitable. No matter how brief, this is better made consciously than subconsciously. Factors considered might include rough estimations of level of consciousness, the expression of "emotions felt" and the maturity of ego (1). If little time remains for covering past medical history, not much is lost. This kind of information is readily obtained by a questionnaire than can be taken home and filled out under conditions more conducive to accuracy of old memories anyway. Patients are eager to participate and their efforts are helpful when directed. Probably the questionnaire should be no longer than can be mimeographed on two letter-size sheets of paper. For the authors it takes the form reproduced at the end of this article. Occasionally, long handwritten expositions are revealing and requests for them may prove therapeutically beneficial as well.

After recording the recent medical history, the temperature, pulse rate and blood pressure are noted (one of a series of readings). Then, if blood screening tests are started, results will be available by the time of a second appointment.

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A great deal can be learned from a 10-milliliter sample of venous blood. When the blood is drawn an hour or so after a meal, a normal value for sugar concentration at this time is good evidence against diabetes mellitus. A photoelectric colorimeter makes this test little more difficult than a Benedict's test of the urine, which then may be omitted. Three milliliters of blood in a Wassermann tube will suffice for a serologic test for syphilis and a complete blood count. Three milliliters in a centrifuge tube will be adequate for determination of clotting time (more or less than twelve minutes), clot retraction (evidence of normal platelets) and total serum protein level (copper sulfate falling-drop method). The remaining 4-milliliter sample of blood is placed in a vial containing 0.4 milligram of potassium and ammonium oxalate for setting up a Wintrobe sedimentation-hematocrit tube, a blood sugar determination (2) and, if desired, a lupus erythematosis cell inclusion preparation (3). To avoid hemolysis, the 1-inch, 22-gauge needle is removed from the syringe before filling these tubes. In the hub of the needle is enough blood for shaking out a small drop through the point onto a cover slip. Stirring the drop briefly with a wooden applicator wet with brilliant cresyl blue stain, colors the reticulocytes. Afterwards, a top cover slip is dropped onto the stained one, and the two are slid apart, allowed to dry, and stained by Wright's or Giemsa's method. With the aid of one assistant, preliminary steps for the blood tests can be performed in about five minutes, including time for filling the pipets and sedimentation tube, making smears, setting the interval timer for one hour (for a single sedimentation reading), and making the hemoglobin determination.

At the end of his first visit, the patient is given a specimen bottle with instructions for the collection of urine. A twelve-hour dehydration sample (fluids withheld after the evening meal, 7 p.m.–7 a.m.) makes specific gravities comparable and meaningful. Furthermore, if instructions for females include discarding the first few drops that pass, a clean specimen more suitable for microscopic study is obtained. Although urinary sugar tests may be omitted if blood sugar determinations are made, microscopic examination of the centrifuged urinary sediment is fully as rewarding to the physician as listening to the heart sounds.

At a second visit, the patient's medical questionnaire can be reviewed and the physical examination completed. This is the visit for action, not words. As the field for investigation narrows, indications for further tests become apparent; meanwhile, a start has been made in performing the chores that in small offices seem so discouragingly time-consuming. Obviously, many variations of the foregoing program suggest themselves for adaptation to individual needs. Part of the art of medicine is an operations research for accumulation of diagnostic data in order to get the *most* information possible, the most *accurate* information possible, at the *least* expense to the patient, and with a *minimum* of wasted time.

MEDICAL HISTORY

Date

Name: Date of birth:
Address: Occupation:

Residence in other cities or countries; give dates:
How far did you go in school?
Past diseases: Give approximate dates and indicate complications.

Regular measles	Tonsillitis	Smallpox
Mumps	Rheumatic fever	Malaria
Whooping cough	Influenza	Typhoid
Scarlet fever	Pneumonia	Diabetes
Diphtheria	Venereal disease	Yellow jaundice
Operations.....	Dates.....	Complications
Injuries.....	Dates.....	Complications
Dates of vaccinations:	Smallpox	Typhoid
Tetanus	Diphtheria	Other

Describe any contact with tuberculosis:

Family history:	Age	Health	Age at death	Cause of death
Father				
Mother				
Bros. and Sis.				

Who in the family has had:
Tuberculosis? Cancer?
Paralysis? Diabetes?
Bright's disease? Epilepsy?
Liver disease? High blood pressure?
Bleeding tendency?
Marital history: Single? Married? Widowed? Divorced?
Age and health of husband or wife?
Ages and health of children?
Habits:
List *all* medicines you now take.
Are there any medicines you cannot take? Why?
Tobacco, how much daily?
Alcohol, amount?
Coffee, cups daily?
Sleep, hours nightly? Insomnia?
Pain:
Are you subject to headaches? At what times?
In what part of the head?
How long do they last?
Do you have chest pain? Location of pain?
What brings it on?
Do you have abdominal pain or discomfort?
Do you have back pain? What part of the back?
At what time of day?
What brings it on?
Gastro-intestinal:
Is mouth or tongue sore?
Is there nausea? Vomiting? Lack of appetite?
Do you eat breakfast?
Do you crave sweets? or water?
Is there "gas and bloating?"
What foods can you not eat? Why?
Number of bowel actions daily? Color?
Looseness? Laxatives?
Genito-urinary:
Is there pain or burning upon urination?
Difficulty in starting the stream? Dribbling?
How many times do you get up to urinate at night?

General:

Do you cough? Type of sputum produced?
Do you have night sweats?
Do you tire too easily? Are you drowsy?
Do you have hot flushes?
Do you have crying spells? Is there mental depression?
Have you recently lost weight? Gained weight?
How much? In what period of time?
Was there ever blood in the sputum? Vomitus? Urine? or stool?
What skin rashes have you had?
Do you have muscle cramps of legs or feet?
Is there numbness or tingling of hands or feet?

For women:

Age at first menstruation? Age at last period?
Are menstrual periods regular? How long do they last?
How far apart are they? (Count from 1st day to next 1st day)
Is there bleeding between periods?
Has there been leucorrhea or discharge? Itching?
If so when and for how long?
Miscarriages?
Complications of childbirth?
Do you have sore breasts?

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DISABILITY OF THE KNEE DUE TO REFERRED PAIN AND RELATED PHENOMENA

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Clinical observations have revealed significant pathologic changes at two sites in the lower part of the back. The abnormalities consist of fibrosis of subfascial fat, with adhesions between this structure and the overlying lumbodorsal fascia. The locations of the alterations are the midsacral paraspinal region and the midlumbar region over the lateral portion of the sacrospinalis muscle (1, 2).

The pathophysiologic effects derived from the lesions are predominantly referred pain and referred tenderness, appearing in the spinal segmental (sclerotomal) distribution of the nerves which receive the impulses at their source. The midsacral site lies within the sclerotomal field of the first sacral nerve; the midlumbar site is supplied by the second lumbar nerve.

At each of the two sites, the tendinous and neuronal elements of the latissimus dorsi muscle are subject to irritation; when this occurs, the referred phenomena are transmitted to the sclerotomal fields of the sixth, seventh and eighth cervical nerves.

Within the scope of somatic nerve effects, three clinical syndromes of pain are recognizable. In addition, autonomic nerve reactions may result from the painful impulses, to intensify the clinical pictures (3). Not uncommonly the process of summation of impulses is operative, to aggravate and prolong the clinical course of trivial injuries.

On the basis of this relationship between the anatomic and the physiologic derangements, a characteristic clinical picture of disability of the knee may develop. The outstanding features are pain on the antero-medial aspect of the knee, less commonly in the lateral portion; onset without known cause or, at times, related to minor injuries; disability due to pain on use, often sufficiently intense to preclude work; absence of objective evidence of serious injury; and moderate to marked tenderness elicited on the antero-medial or antero-lateral aspect of the joint and extending above and below the joint line for a distance of 2 or 3 inches.

The diagnosis is made from the pattern of distribution of the referred pain and tenderness, together with demonstration of a significant degree of tenderness at the sites of the pathologic lesions, or trigger-points, in the sacral and lumbar regions. The diagnosis is confirmed by the response to injection of local anesthetic into the pathologic tissues (4).

Treatment consists, in principle, of interruption of painful impulses arising in the subfascial structures of the back. In some instances, satisfactory results are obtained by local anesthetization of the trigger points. As a rule, surgical correction is necessary for complete and lasting relief.

According to Inman and Saunders (5), the first sacral nerve provides scle-

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rotomal innervation to musculoskeletal structures in the buttock, thigh, leg and foot; in the region of the knee this nerve supply includes both superficial and deep components.

CASE REPORTS

Case 1. This 32-year-old man, a veteran of World War II, was examined for a service-connected disability of the back and the left knee. Due to constant pain, progressing in intensity, he had had to discontinue work as an upholsterer, three weeks previously.

Examination of the back showed a moderate degree of limitation of motion accompanied by pain. Mild tenderness was elicited in the left midsacral region, where a nodular mass of soft tissue was palpable.

In the left knee the pain was located by the patient on the antero-medial aspect of the joint. Moderate tenderness was elicited over the joint line, in the femur above, and in the tibia below this level. Motion of the knee was normal in range and somewhat painful. No other abnormality was noted.

On the following day, the nodular mass in the left sacral region was anesthetized by infiltration of the subfascial tissues. Within ten minutes after this was completed, he was free from the pain in the back and motions were normal and painless. He also noted a considerable reduction of the pain in the left knee.

He was re-examined three hours later. He was completely free from all pain, and the tenderness in the left knee had been eliminated. The symptoms later returned to their former intensity. No further observation was possible.

Case 2. This 51-year-old housewife gave the following history: At the age of 19, she sustained an athletic injury to the neck in which "a small piece of bone was broken off." A fragment of bone was later removed surgically. Since then she had experienced frequent headache, pain and weakness of the left arm and hand, and numbness of the left hand on use. Her neck felt stiff and painful so that she could not move it freely.

Seven years before, the left knee became painful without injury or known cause; sometimes pain was experienced in the left buttock.

Examination of the neck showed a moderate restriction of motion due to pain at extreme ranges. In the midline posteriorly, a surgical scar was noted extending from the sixth cervical to the second dorsal levels. Tenderness was elicited in the cervico-dorsal region on both sides of the midline; from the left side, the pain was described as radiating downward toward the left hip. Moderate tenderness was also found in the left infraspinatus and latissimus dorsi muscles and in the suprascapular region on both sides. In the left hand the skin was hypoesthetic to pin-prick and pinching.

In the left knee, the only abnormality was a moderate degree of tenderness on the antero-medial aspect, involving the joint line, the lower end of the femur and the upper end of the tibia, over a length of 3 to 4 inches.

At the level of the third sacral segment on the left, moderate tenderness was elicited, with pain described as radiating to the scapula on both sides.

From these findings it was considered likely that the left midsacral region represented the trigger point for the pain in the knee (first sacral nerve syndrome) and that the clinical features in the upper parts of the body represented the latissimus dorsi syndrome, the source of which was also in the left midsacral area.

The left midsacral paraspinal region was injected with procaine, subfascially and intrafascially, to anesthetize also the elements of the latissimus dorsi muscle.

Two hours later the patient stated that the pain in the knee was noticeably reduced. The site was re-injected.

After another period of two hours, she stated that all pain in the left knee and the lower part of the back was eliminated. No tenderness was found in the knee. In the upper part of the back, the tenderness of the cervico-dorsal region had been abolished and motion of the neck was normal.

On re-examination nine months later, she was completely relieved of all pain in the left knee and the left buttock. In the upper portions of the body, she had been relatively free

from discomfort for four months after the injection. The pain had recurred, though it was less intense than formerly. The only significant finding was tenderness in the suprascapular muscles, evidently the supraspinatus and trapezius.

Comment: The observations in this case indicate a disability of long duration. The combination of two syndromes arising from the same source is not unusual; it is a development of referred phenomena arising from a pathologic structure in which deep somatic tissues supplied by different spinal nerves are irritated, thus giving rise to two separate streams of impulses proceeding in opposite directions. In this patient, the clinical manifestations of the first sacral and the latissimus dorsi syndromes were appreciably relieved. The residual pain and the tenderness noted at re-examination were evidently caused by other disorders, probably irritation from the site of the injury and the subsequent operation.

Case 3. A 67-year-old widow, employed as a milliner, was examined for pain in both knees, mild in the left but severe and disabling in the right. This pain had its onset about four weeks previously, without injury or known cause except a possible strain during a heavy shopping season. She had been treated elsewhere for "arthritis," spending eleven days in the hospital. She was greatly handicapped in going up or down stairs, in entering and leaving automobiles, or walking on icy surfaces, and was able to walk only about a fourth of a mile under favorable conditions.

Examination of the right knee disclosed moderate to marked tenderness on the antero-medial aspect of the joint, for about 2 inches upward on the femur and 3 inches downward on the tibia. No other significant abnormality was found in the lower extremities. Examination of the back showed a moderate degree of tenderness in the right midsacral region, but otherwise no abnormality.

The site of tenderness in the right sacral area was believed to be the trigger point for the pain in the knee. An exploratory operation, under local anesthesia, revealed numerous fibrous connections between the ventral surface of the lumbodorsal fascia and the subfascial fat tissues. The adhesions were dissected from the fascia and a layer of fibrotic subfascial tissue was resected to a depth where the fat tissue appeared normal. A soft rubber drain was inserted into the operative field, to be left in place for from five to seven days.

The patient was promptly relieved of the intense pain in the right knee, permitting more activity and restoring function so that she resumed work at full time three weeks later. She continued work for about three months. During observation for six months, there has been no recurrence of the pain or other disorder related to the pathologic changes in the sacral region.

Case 4. A 75-year-old plumbing contractor was examined in the out-patient department of the hospital. Two days previously he had experienced a sudden attack of pain in the left knee, without injury or known cause. The pain progressed in severity so that he became bedfast at home. He was transferred to the hospital by ambulance.

Examination: The left knee was supported in partial flexion on a pillow; any movement, active or passive, caused severe pain. The pain was located by the patient on the lateral aspect of the knee. Tenderness was very pronounced, extending for a distance of 2 or 3 inches above and below the joint line. There was mild tenderness also on the antero-medial aspect of the knee.

On examination of the back, in the left midsacral paraspinal region there was a site of mild hyperalgesia on moderately heavy pressure; in association with this, the patient described pain radiating downward to the knee.

The tender site in the left sacral region was infiltrated subfascially with 5 cc. of procaine.

About five minutes later the patient was able to move the knee actively. Within ten minutes after the injection, he was able to sit up and extend the knee. He described his condition by stating that "the grinding pain is gone," "the leg feels warm now" and "the needles sensation in the foot has disappeared."

One hour later he was taken to his home by automobile. He reported that he walked into the house unassisted, also climbing several flights of stairs. He resumed his regular work three days later, completely relieved. There has been no recurrence during an observation period of four months.

Comment: In this case the disability was more complete. The location of the pain was on the lateral aspect of the joint, whereas in the other cases it was most marked in the antero-medial portion of the knee.

DISCUSSION

The clinical pictures noted in these cases are characterized by uniformity in the location of the principal features and by the absence of other significant findings expected in disabilities of this magnitude. The degree of the handicap is indicated by the fact that 3 of the 4 patients were incapacitated for work. It is noteworthy also that 3 of the patients were treated elsewhere for "arthritis."

The anatomic abnormalities of the lumbodorsal fascia and the subfascial structures develop with great regularity at two distinct sites. There is reason to believe that they have their onset in the early years of life and remain in an inert condition for indefinite periods of time (6). The structural appearance and relationships at the two locations are similar.

The pain mechanisms associated with the two sites of injury in the back differ somewhat in their relationship to disorders of the knee. When the clinical features are due to a lesion in the sacral area, the pathophysiologic process is one of referred (sclerotomal) pain and tenderness; in this process there may be a summation of impulses to intensify the symptoms. In some instances, the lesion in the lumbar region also participates in the pain mechanism; since this lesion lies in the second lumbar nerve field, which does not innervate any portion of the knee, harmful effects on the knee are probably due to autonomic nerve reactions.

Local anesthesia is used primarily as a diagnostic procedure. It is, however, not unusual to find that relief is maintained for indefinite periods of time (4).

SUMMARY

From an anatomic lesion in the midsacral paraspinal region, pain and tenderness may be referred to other portions of the first sacral sclerotome. A characteristic clinical picture of referred pain to the knee may develop from structural abnormalities of the lumbodorsal fascia and the subfascial tissues. Local anesthesia by infiltration of the subfascial space in the sacral region is employed as a diagnostic measure and, not uncommonly, provides substantial or complete relief of symptoms. In some instances, surgical correction is indicated.

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PREMATURE VASCULAR DEGENERATION IN DIABETES MELLITUS: PATHOGENESIS, AND RELATION TO AGING

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INTRODUCTION

Arteriosclerosis is probably a structural result of a physiologic disorder. The underlying physiologic basis for arteriosclerosis is being sought by many. There is growing evidence that hormones may be one of a wide variety of factors related to the pathogenesis of arteriosclerosis. Not only gonadal hormones (1–4), but also hormones from the thyroid, pituitary, adrenal cortex and pancreas may be involved in the production of, or protection from arteriosclerosis.

One approach to the problem of arteriosclerosis would be to study diseases in which the physiologic disorder is known and in which there is a propensity to premature vascular degeneration. If we can understand the metabolic basis for premature arteriosclerosis in these diseases, we may find a clue to some of the causes of arteriosclerosis in general.

The premature arteriosclerosis produced by adrenocortical hormones in Cushing's syndrome was discussed in a previous report (5).[1] It was suggested also that adrenocortical hormones may play a role in the production of arteriosclerosis in some aging people without Cushing's syndrome.

The premature vascular degeneration observed in association with insufficient insulin therapy in diabetes mellitus affords another opportunity for gaining insight. There may be some common physiologic denominator for the arterial degeneration occurring in Cushing's syndrome, "insulin-deficient" diabetes, and aging. After certain aspects of the pathogenesis of arteriosclerosis in Cushing's syndrome are reviewed briefly, a theory for the pathogenesis of vascular degeneration in "insulin-deficient" diabetes will be proposed.

PATHOGENESIS OF ARTERIOSCLEROSIS IN CUSHING'S SYNDROME AND IN "INSULIN-DEFICIENT" DIABETES

Cushing's syndrome

It has been emphasized that premature arteriosclerosis occurs in Cushing's syndrome (5) and is probably due in part to: 1) lack of proper protein maintenance of blood vessel walls secondary to excess antianabolic (or catabolic) hormones from the adrenal cortex, and 2) deranged lipid metabolism due to excess adrenocortical hormones.

The bruisability and increased capillary fragility in Cushing's syndrome probably result from a weakness of blood vessel walls caused by excess adreno-

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cortical antianabolic hormone (5). This hormone prevents the synthesis of body protein from protein-precursors (6), such as amino acids, and may even cause a breakdown of body protein with the ultimate formation of glucose. For this reason, it is referred to frequently as the gluconeogenic hormone, glucocorticoid, or "S" hormone of Albright—the "S" standing for sugar production. In the presence of an excess of this hormone, there is a general wasting of the protein tissue throughout the body (5), giving rise to osteoporosis, weak skin and resultant large striae, decreased muscle and decreased creatinine excretion. Very likely the protein tissue of the blood vessels is seriously affected. Sclerosis and calcification of arteries may be an attempt to strengthen blood vessel walls when protein is not available (5). Excess anti-anabolic hormone interferes with protein biosynthesis, causing protein to be unavailable for maintaining normal blood vessel structure and strength. "Hardening of the arteries" may be a compensatory process to prevent "weakened" and "softened" vessels from bursting, leaking, or bulging.

In the medial sclerosis of Monckeberg, it has been said that calcification of the media is preceded by fatty degeneration (7, 8). Fatty degeneration has been demonstrated in the media of arteries in Cushing's syndrome (9). To recapitulate the order of progression: excess antianabolic hormone—wasting of protein tissue in blood vessels—fatty degeneration—calcification and sclerosis.

Thewlis has discussed the anatomic changes called senescent degeneration (10): "A wasting of tissue which is either not repaired at all or is replaced by tissue of a different character." In both Cushing's syndrome and in aging the "high-grade" protein of arteries wastes (5) and is often replaced by other tissue "of a lower order" and inferior function.

"Insulin-deficient" diabetes

In "insulin-deficient" diabetes there seems to be evidence of a similar weakness of blood vessels (11), namely: 1) hemorrhages in the fundi, 2) capillary aneurysms in the fundi, and 3) increased capillary fragility (12–15).

From the viewpoint of protein anabolism and catabolism, the effect of insufficient insulin is similar to that of excess glucocorticoids. The action of insulin is protein-anabolic, whereas that of the glucocorticoids is protein-antianabolic. Lack of insulin has a marked protein-antianabolic effect; excess glucocorticoids also have this effect. Therefore, it is not surprising to find some similar lesions in a syndrome associated with *excess* glucocorticoids and in a disease due to *insufficient* insulin. Salter and Lawrence in experiments demonstrating the profound protein-anabolic action of insulin, also demonstrated that cortisone prevents the growth effect of insulin (16).

Best (16) emphasized strongly that insulin is a very important anabolic hormone—probably the most important anabolic hormone in the body: "The evidence is accumulating that insulin is a central anabolic hormone without which many of the building processes sometimes attributed entirely to other hormones, cannot proceed at a physiologic rate. Indeed, this is self evident

when we recall the devastating catabolic effects of pancreatectomy in many species, their complete relief by insulin, and the fact that the loss of no other single hormone produces more widespread catabolic derangements."

When there is a deficiency of insulin, the protein tissues of the blood vessel walls may suffer as they do in Cushing's syndrome (5) and arteriosclerosis may be the end-result. This process would involve blood vessels of all sizes. Generalized vascular degeneration occurs in diabetes (17), and may well be related to "protein starvation" of the blood vessel walls. Bell has shown involvement of the arteries, arterioles and capillaries in diabetes (18). Early alterations in the circulation in the digital vascular bed have been described (19), and vascular changes in the conjunctiva (20) and nail bed have been found. Veins apparently do not escape involvement (21, 22).

Those diabetics who suffer from both lack of insulin and hyperadrenocorticism (*i.e.*, excess glucocorticoids) should have doubly severe vascular degeneration. Becker (23) adduced evidence strongly suggesting that diabetics with severe retinopathy and Kimmelstiel-Wilson lesions often have a combination of relatively increased adrenocortical activity and diabetes. He indicated that diabetics with a compensatory decrease in adrenocortical capacity have less retinopathy and Kimmelstiel-Wilson lesions.

AGING, ARTERIOSCLEROSIS, AND DIABETES—ALL CATABOLIC CONDITIONS

Though people often become fat as they grow old, aging seems to be a catabolic process as far as "high-grade" protein tissue is concerned. For instance, muscle mass progressively diminishes after the age of twenty-five (24). A good farmer recognizes a very old horse at a glance by noticing the sunken temples which represent decrease in the size of the temporal muscles. Very old people frequently have wasting of the interosseous muscles, giving their hands a characteristic appearance ("guttering"). If aging itself is a type of protein catabolism (or a decreasing protein anabolism), is it any wonder that arteriosclerosis occurs prematurely in the protein-catabolic environment of diabetes? Insulin, the anabolic hormone par excellance, might be considered an "anti-aging" hormone.

It has been said that a person is as old as his arteries. It might better be said that a person and his arteries are as old and degenerated as his "high-grade" protein tissue (muscle, elastin (25), bone matrix, endothelium or epithelium). Since the normal maintenance of "high-grade" protein tissue is dependent on insulin, (as well as other factors), it seems logical that lack of insulin may lead to premature aging and premature arteriosclerosis.

FURTHER CONSIDERATIONS ON THE RELATIVE IMPORTANCE OF INSULIN AND PROTEIN METABOLISM IN DIABETIC ARTERIOSCLEROSIS

Not only insufficient protein anabolism, but also deranged fat and carbohydrate metabolism play a part in the pathogenesis of vascular degeneration. For instance, there is a hyaline alteration in and around the smaller blood vessel walls in diabetes; and this may be related to an excess formation of polysaccharides and mucopolysaccharides (26). These polysaccharides may be

laid down in relation to the vessel walls and have the microscopic appearance of hyaline. If a quantitative analysis of all the blood vessels of some diabetic patients were made, there would probably be an increase of polysaccharides, lipids and calcium, and a decrease in "high-grade" protein. This change would be a decadent one.

In addition to the adverse effects of insufficient insulin, a deficiency of vitamins (*e.g.*, C, P or B_{12}), enzymes and minerals may play a role in the production of premature vascular degeneration. Diets high in refined carbohydrates not only predispose people with an hereditary tendency to diabetes to insufficient insulin for protein anabolism, but also result in a dearth of vitamins, minerals and other essential substances. Methionine, an essential amino acid found in "high-grade" protein food, is a lipotropic agent and may conceivably help prevent atherosclerosis in primates (27).

It is of interest that in studying the relationship of serum lipids to atherosclerosis, emphasis has shifted from serum cholesterol to lipo*proteins* (3). It would seem that lipids and proteins in the serum are related to atherosclerosis. Although serum lipoproteins are related to atherosclerosis, it has not been shown that this is a causal relation. It may be that abnormal serum lipoprotein levels merely reflect an underlying disturbance in lipid and protein metabolism. Perhaps these underlying disturbances in lipid and protein metabolism, rather than the abnormal lipoprotein levels themselves, produce atherosclerosis. One way in which disturbed protein metabolism may give rise to arteriosclerosis has been described here, namely, decreased protein synthesis or increased breakdown.

A decrease in the concentration of serum protein [(28); albumin (29, 30)] sometimes occurs in diabetes. Serum albumin may be important in preventing disturbed lipid transport in the blood (31). The ratio of albumin to the various globulin fractions in the blood may have a bearing on the sludging of blood (and increased sedimentation rate) which occurs in diabetes. Sludged blood may be an added cause of vascular degeneration in diabetes (20, 32). It might be illuminating to investigate further the serum proteins, including their electrophoretic patterns, in patients with different clinical types of arteriosclerosis. A decreased serum albumin level has been reported in "normal" aged individuals (33) as compared with younger age groups.

The significance of defective protein anabolism as a cause of premature vascular degeneration in diabetes has been stressed here. It is not the intention in this paper to claim that deficient protein anabolism is the only cause of premature arteriosclerosis in diabetes. However, this aspect of the relationship of diabetes to premature arteriosclerosis probably should receive more attention than it has in the past.

DISCUSSION

The group at the New England Deaconess Hospital (34, 35) and others (36, 37) have shown statistically that strict, excellent control of diabetes prevents or delays the onset of degenerative vascular lesions. These statistics would be

even more convincing if additional theory were offered to explain the beneficial effect on the arteries of such treatment. Perhaps the theory here propounded at least partially fills the need; for if insulin insufficiency causes premature arteriosclerosis by a protein-antianabolic (or catabolic) effect, then giving sufficient insulin logically should prevent or delay the onset of premature arteriosclerosis.

The scientific method involves gathering facts, then making a theory that will explain these facts and then using the theory to find new facts. If the theory is wrong, but leads to the discovery of new facts, the theory has not been useless. The theory expounded here calls for confirmation by direct study of the metabolism of the blood vessel walls. This is a practical job that should be carried out. If this paper accomplishes no more than to encourage someone to study the metabolism of blood vessels, it will have been worth while.

SUMMARY

Premature arteriosclerosis occurs in both diabetes due to hyperadrenocorticism and in "insulin-deficient" diabetes.

The action of glucocorticoids from the adrenal cortex is protein-antianabolic or catabolic. Excess glucocorticoids (as in Cushing's syndrome) cause a wasting of protein tissue throughout the body. The protein tissue of blood vessel walls is probably involved too. Fatty replacement, calcification, and sclerosis may follow in the wake of degeneration of protein tissue in the vessel walls.

Insufficient insulin also causes antianabolic or catabolic derangements affecting the protein tissue of the body. Here again, the protein tissue in the blood vessel walls may suffer and be replaced by tissue of a different character. This may give rise prematurely to anatomic changes of senescent degeneration—*i.e.*, arteriosclerosis.

Aging itself is a type of protein catabolism or a decreasing protein anabolism; therefore it is not surprising that arteriosclerosis occurs prematurely in the protein catabolic environment of diabetes.

Protein antianabolism or catabolism is not the only mechanism of production of arteriosclerosis in diabetes. However, this aspect of the relationship of diabetes to premature arteriosclerosis should receive more attention.

This concept may help to explain why giving optimum amounts of insulin to diabetic patients prevents or delays the onset of vascular degeneration.

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FACTORS INFLUENCING PROGNOSIS IN PSYCHIATRIC ILLNESS OF THE AGED*

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This report is based on a follow-up study of 200 patients over 60 years of age who were hospitalized in a private psychiatric sanitarium during the years 1950–52. The subsequent course of these patients in terms of clinical progress and social adjustment was followed for a two-year period. All available information was analyzed with a view toward correlating the medical, psychologic, sociologic and psychiatric data with later outcomes, whether favorable or unfavorable.

The patients in this series are drawn from the populous urban and rural area of southeastern Michigan and are typically upper middle-class people from a wide variety of social, vocational and religious backgrounds. One Negro is included in the group. These individuals are representative of the type of elderly patients who are referred to private psychiatric facilities when a mental disorder of either acute or chronic nature is beyond the control of the family and the medical facilities of the home community. Short-range psychiatric hospitalization is sought, often on an emergency basis, with the hope of returning the patient home if rehabilitation is possible, or for assistance in a program of care if long-range placement will be required.

CLASSIFICATION OF OUTCOMES

The crucial issue in the outcome of mental illness in the aged appears to be determined almost entirely by the ability or inability of the patient to return to his former life and make a reasonably acceptable adjustment to it. It was found that when clinical outcomes were graded in this way they fell naturally into four groups, two favorable and two unfavorable, as follows:

Group I: Patients who continue much improved or recovered, whose relatives confirm the report that they are capable of managing their own affairs as well or better than before, and who are occupied in some part-time or full-time work, have interests in some avocation and take part in social activities of their community.

Group II: Patients who are improved and able to live at home, but who require special attention for minor or non-disabling infirmities or defects of physical, mental or emotional nature, which interfere to a considerable extent with the full range of activities mentioned in Group I.

Group III: Patients who have major disabilities or defects in their mental and emotional health, with or without accompanying physical or neurologic disability, such that they require considerable supervision and care in order to maintain a minimal adjustment in their own home or in some private nursing or convalescent institution.

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Group IV: Unimproved patients who are totally unable to manage for themselves and who require constant custodial-type supervision, either in a suitable nursing home or in a state mental hospital. Irreversible, progressive degenerative dementias are included in this group.

Some fifteen factors related to premorbid personality, the apparent precipitating cause of the mental illness, the treatment used, and the quality of aftercare, were evaluated at the end of the two-year observation period. The factors selected for presentation here are those which permitted some type of objective measurement. Data from the hospital records were pooled with all information available to the psychiatrist and the psychiatric social worker, as gained by continuing contacts with the patients and their families up to the present time.

AGE AND SEX DIFFERENCES

The study group consisted of 82 males (41 per cent) and 118 females (59 per cent). The age range was from 60 to 93 years, the average being 66⅓ years and the mean, 65 years. Of the 200 patients, 71.5 per cent were between the ages of 60 and 70 at the time of admission to the hospital, and the remaining 28.5 per cent were over 70 (Table 1).

Fifty-one per cent of the patients with a favorable outcome (Groups I and II) were below the age of 65 when admitted, and 44.4 per cent were between 65 and 75, after which the favorable outcomes dropped to 4.7 per cent. Of the patients with unfavorable outcomes, 41.5 per cent were below the age of 65 at the time of admission, 41.4 per cent were between 65 and 85, and 17.1 per cent were admitted after the age of 75.

For the group as a whole, 106 (53 per cent) had favorable outcomes, and 94 (47 per cent) had unfavorable outcomes. Thirty-four (41.4 per cent) of the 82 males in the group had a favorable outcome, and in 48 (58.6 per cent) the outcome was unfavorable. Similarly, of 118 females in the total series, 72 (61 per cent) had favorable outcomes, and in 46 (39 per cent) the outcome was unfavorable. When a comparison was made between sexes, the female patients had a consistently better prognosis in all age ranges.

OUTCOMES IN RELATION TO DIAGNOSIS

Of the ten diagnostic groups shown in Table 2, senile and arteriosclerotic psychoses make up 27 per cent. Functional and affective disorders (involutional

TABLE 1

Ages at Admission

Age range	Males	Females	Total	Per cent
60–64 years	38	55	93	46.5
65–69 years	18	32	50	25.0
70–74 years	13	23	36	18.0
75–79 years	4	3	7	3.5
80 years and over	9	5	14	7.0
Total	*82*	*118*	*200*	*100.0*

TABLE 2

Outcomes

Diagnosis	Favorable	Unfavorable	Total	Per cent
Senile psychosis	1	17	18	9.0
Cerebral arteriosclerosis	11	25	36	18.0
Involutional psychosis	36	19	55	27.5
Manic-depressive psychosis	12	16	28	14.0
Depressive reaction	35	6	41	20.5
Psychoneurosis	6	2	8	4.0
Alcoholic psychosis	4	1	5	2.5
General paresis	0	3	3	1.5
Organic psychosis	1	1	2	1.0
Schizophrenia	0	4	4	2.0
Total	*106*	*94*	*200*	*100.0*

psychoses, manic-depressive psychoses, depressive reactions and other psychoneuroses) make up 66 per cent. The remaining 7 per cent consisted of toxic and organic disorders, and 4 cases of schizophrenia.

Senile and arteriosclerotic cases grouped together had favorable outcomes in only 6 per cent, as contrasted to 44.5 per cent in the involutional-affective-psychoneurotic group. Manic-depressive patients presented some difficulty in final classification, 3 having had recurrences during the observation period; but on an overall basis, 12 outcomes were considered favorable and 16 unfavorable in terms of clinical outcome. The unexpectedly high number of unfavorable outcomes in the affective group was undoubtedly the result of superimposed arteriosclerotic features which overshadowed the original recurrent functional disorder.

PERSONALITY FACTORS

Background information in the case histories revealed that 81.5 per cent of the patients in this series had made satisfactory social adjustments, and 92 per cent had made good vocational adjustments before hospitalization. There was evidence that major family and marital problems had occurred during the lifetime of some 35 per cent. Outcomes in this group were evenly divided between the favorable and the unfavorable, and there was no difference between the sexes in relation to the factor of background psycho-social difficulties.

Examination of the marital status at the time patients were hospitalized showed that 55.5 per cent of the entire group were married, 29.5 per cent were widowed or divorced, and 15 per cent had never married. It was found that of 30 patients who married, but had no children, 21 were still married, 8 were widowed, and 1 was divorced. When the 30 single patients (5 men and 25 women) were added to this number, it was noted that 60 or 33.3 per cent of the total group had never experienced parenthood.

As indicated in Table 3, the ratio of favorable to unfavorable outcomes for 17 childless males was approximately 1:3, whereas for 43 childless females it was 3:2 ($X^2 = 4.5$, revealing significance at the 5 per cent level). Favorable out-

TABLE 3

Outcomes in childless patients

Marital status	Favorable		Unfavorable		Total	
	M	*F*	*M*	*F*	*M*	*F*
Married	2	9	6	4	8	13
Single	2	14	3	11	5	25
Widowed	0	2	3	3	3	5
Divorced	0	0	1	0	1	0
Total	*4*	*25*	*13*	*18*	*17*	*43*

comes occurred in 58.1 per cent of the childless females, and in only 23.5 per cent of the childless males. This factor thus appears to be related to unfavorable outcomes only in the males. It is to be noted that the number of individuals who had not experienced parenthood was unusually high in this group of patients, in contrast to the proportion in the general population. It is estimated by sociologists that on the whole not more than 19 per cent of the population in the Central States region fall into the childless group.

Long-standing personality problems classifiable as chronic psychoneurotic, psychotic, and character disorders were observed in 36.5 per cent of the group. These personality problems appeared to be evenly divided between the favorable and the unfavorable outcome groups, hence it would not appear that this factor by itself is statistically helpful in differentiating patients who are more likely to have more successful responses to treatment.

Previous psychiatric treatment on an out-patient basis was given to 13.5 per cent of the patients, and psychiatric hospitalization occurred in 31 per cent before 1950–52. Twenty-three (28 per cent) of the males and 39 (33 per cent) of the females received previous psychiatric treatment in sanatoria and mental institutions. Among the favorable outcome group 47.1 per cent had previous treatment (in-patient, out-patient, or both), and among the unfavorable group this value was 41.5 per cent. As might be expected, the functional and affective group accounted for 80.6 per cent of the previous psychiatric hospitalizations, whereas among the senile and arteriosclerotic group of 54 patients, there were only 7 (13 per cent) who received such care previously.

PRECIPITATING FACTORS

As far as opinions and judgments based on case history material can be deemed reliable, the three most important factors leading to the onset of psychiatric illness in this group were family conflicts, threat of disability, and affective deprivation.

Acute family or marital stress was present at the time of admission in 49.5 per cent of the cases. There appears to be no significant difference in the incidence of this factor in males or females or among favorable or unfavorable outcomes.

Fear and anxiety related to threat of disability from disease or impairment of health was reported as a factor in 33.5 per cent of the cases, the value being 39.6 per cent for favorable and 26.6 for unfavorable outcome groups, and 29.2 per cent for males and 36.4 per cent for females. Gross screening of all medical examinations revealed the incidence of actual major physical illness to be 28 per cent for the entire group; it was 18 per cent for the favorable and 39.3 per cent for the unfavorable outcomes. Although the two do not coincide, it is interesting that the patient's fears of disability roughly paralleled the overall incidence of physical disease in this particular group of elderly patients.

Affective deprivation from the loss of loved individuals by death or separation occurred as a factor in the onset of mental illness in 31.5 per cent of the patients. Accurate evaluation of an influence of this nature on different individuals is impossible, but it seemed to occur in 41.6 per cent of the females, in contrast to 19.5 per cent of the males. It was also found to be 14 per cent higher in the favorable than in the unfavorable outcome groups.

FACTORS IN TREATMENT

Regardless of outcome, treatment of the mentally ill older patients by skilled medical and nursing personnel is of great aid with respect to re-establishing a regular routine of daily habits and activities. Along with improvement of nutrition and treatment of the general physical condition, these patients all received Metrazol (0.1 Gm. three times daily) as well as daily supplementary vitamins. Success of the nurses' efforts to give training in satisfactory self-care is often of determining importance in later placement plans for the patient. Better understanding on the part of relatives is of equal importance in the after-care, even in the group having the least favorable prognosis, and may often delay or make state hospital commitment unnecessary.

Besides its specific value in depressive disorders, electrotherapy is often definitely helpful in controlling disturbed mental states and food refusal when patients are first admitted to the hospital. This form of treatment was employed in 148 patients (78.5 per cent) of this series. Of these, 89 (60.1 per cent) had favorable outcomes. Equal numbers of both improved and unimproved senile and arteriosclerotic patients received electroshock without untoward event. Of 52 who were not given electroshock, 17 (32.7 per cent) had favorable outcomes.

Efforts to give insight were felt to be at least in some degree helpful to 46.5 per cent of the patients, and follow-up studies revealed that 59.4 per cent of these were in the favorable and 32.0 per cent were in the unfavorable categories. It is estimated that in some 71.5 per cent of cases, relatives were able to gain better understanding of the patient's illness and needs with respect to care after discharge from the hospital.

OUTCOMES AT END OF TWO-YEAR PERIOD

Follow-up information revealed that of the 106 patients in the favorable category, 89.6 per cent were living with their families at the end of the two-year period. Seventy-five per cent reported they were doing some type of full

or part-time work. Eighty-two per cent regarded their general physical health as satisfactory. Hobbies of some kind were mentioned by 72.2 per cent, and 90.5 per cent indicated continuing interest in social and community activities. This convincingly reaffirms the fact that the universal need for satisfying personal, social, and emotional experiences applies no less to the recovered mentally ill than to all individuals in the sixth to eighth decades.

On the unfavorable side, 15 men and 16 women were committed to state hospitals during the two-year study period, constituting 15.5 per cent of the original series. The remaining 34 of the 65 patients in the unfavorable (Group IV) category required custodial care in various private institutions and nursing homes.

Forty-four (22 per cent) of the 200 patients died within two years after they left the sanitarium—33 per cent of the males and 15.2 per cent of the females. The average age at death was 69 years, 3 months. The survival time of these 44 patients ranged from less than one month to thirty-six months, the average being eight to nine months after leaving the hospital. Twenty-seven of the deaths were among the senile psychotic and cerebral arteriosclerotic groups, which constituted half of the original number.

Three men and 1 woman committed suicide; 2 were in the manic-depressive and 2 in the depressive reaction categories. The average age at death for these 4 patients was 64 years.

SUMMARY

1. In a follow-up study of 200 hospitalized elderly psychiatric patients, it was found that at the end of a two-year observation period, females had a consistently better prognosis than males in all age ranges between 60 and 90 years.

2. Outcomes were favorable at the end of the two-year period in 51 per cent of patients who were between 60 and 65 years of age at the time of admission. In the affective, involutional and psychoneurotic groups, favorable outcomes occurred in 63 per cent.

3. Outcomes were favorable in only 6 per cent of senile and arteriosclerotic patients. Half of the 54 patients in these two diagnostic groups died within nine months.

4. The psychologic factors which appeared to be of greatest importance in the precipitation of mental illness were family conflicts, threat of disability, and affective deprivation.

5. The proportion of patients in this series who had not experienced parenthood was almost twice that in the general population, and childlessness as a factor was related to poor prognosis, especially in males.

6. Sex, age and diagnosis remain the three most consistent factors influencing favorable or unfavorable prognosis in mental illness requiring psychiatric hospitalization in individuals past 60 years of age.

ACUTE SMALL-BOWEL OBSTRUCTION

JOHN A. BOLLINGER, M.D. AND LUKE W. NABERS, M.D.

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The incidence of acute small-bowel obstruction is increasing, apparently due in large part to the increased incidence of adhesion bands, in association with the increased survival rate of the present-day patient and the increased number of laparotomies (1). Fortunately, the mortality from this acute condition of the small bowel has continued to fall as a result of the use of intestinal decompression tubes, antibiotics, more knowledge of the control of fluid and electrolytes, and the availability of blood for transfusion (2). The mortality rate in the past ten years has been between 8 and 16 per cent compared to the mortality rate of 60 per cent reported by Scudder forty-six years ago (3, 4, 5).

In a review of 221 cases from 1945 to 1953, the diagnosis was verified at autopsy or surgical intervention in 185. In the remaining 36 there was a response to conservative therapy but they showed all the criteria of acute small-bowel obstructions due to adhesion bands (1). Neurogenic ileus was not included in this study. It was interesting to note that of the 221 patients 69 (31 per cent) were over 60 years of age, the oldest being 93. The etiology of the obstruction in these cases is compared to that of the overall age groups in Figure 1.

Although the etiology in the advanced age group generally follows that of the entire group, the diseases which usually occur in older persons (incarcerated herniae, mesenteric thrombosis, and gallstone ileus) account for the relatively higher incidence in the 60-plus patients.

Probably the first factor which reflects the mortality is the underlying pathologic process which is the cause of the acute obstruction. The greatest surgical mortality is recorded in mesenteric thrombosis (75 per cent) and in neoplasm (25 per cent). Congenital defects, adhesions, regional ileitis, and gallstones follow in the order mentioned.

In the same vein, the extent of the surgical procedure to be performed is governed by the pathologic process found by the surgeon. The pathologic picture is not solely determined by the etiologic agent but is also influenced by the patient's delay in seeking medical aid or the doctor's delay in instituting the correct therapy. A marked rise of the mortality as a result of delay is noted after forty-eight hours (Fig. 2). Electrolyte and fluid reserves are depleted during the delay, and operation may have to be performed on a patient with little or no physiologic reserve, compounded with advanced pathologic changes. The effect of the previously mentioned progression of events is clearly shown by the relationship of the operative procedure to the mortality (Fig. 3).

In obstruction from adhesion bands, persistence of conservative therapy with a long intestinal tube contributes to the mortality. Obviously, surgical intervention is indicated when signs of strangulation appear, but the timing of inter-

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vention after a period of unsuccessful conservative therapy is not as clear as that for strangulation. The progress of the patient is carefully followed clinically, by x-ray examination of the abdomen, and by checking the overall physiologic state.

One of the methods employed by the author to aid in the determination of the degree of the obstruction is the oil-enema routine. A 2-ounce portion of mineral oil is injected into the decompression tube, which is clamped for one hour. If the obstruction is partial, the oil can be recovered by enema two to six hours later. Should the oil not be recovered, one may assume that the obstruction is complete, and resort to surgery, since further conservatism will probably be unfruitful. This procedure was carried out in 51 cases without any deleterious effects.

In Figure 4 is shown the final roentgenogram after twenty-four hours of conservative therapy, revealing a persistent distended small intestine. After the oil-enema routine (which did not show oil rectally) and the absence of adequate improvement in twenty-four hours, the patient was subjected to laparotomy prior to deterioration of her condition. An adhesion band bound the upper portion of the ileum to the posterior peritoneal wall and resulted in a complete obstruction which could not possibly have been relieved by conservative means. The oil-enema routine may also reinforce one's decision to remove the decompression tube after a period of successful intestinal decompression, especially when it is feared that the marked improvement may only be due to the action of the suction tube and that the point of obstruction has not actually been passed.

In cases in which the long intestinal tube is used unsuccessfully, the timing of the surgical intervention is not clear; thus, one should limit the period of unsuccessful conservatism. Such a schedule should be determined by the clinical condition of the patient but it can and should be more specifically stated, as

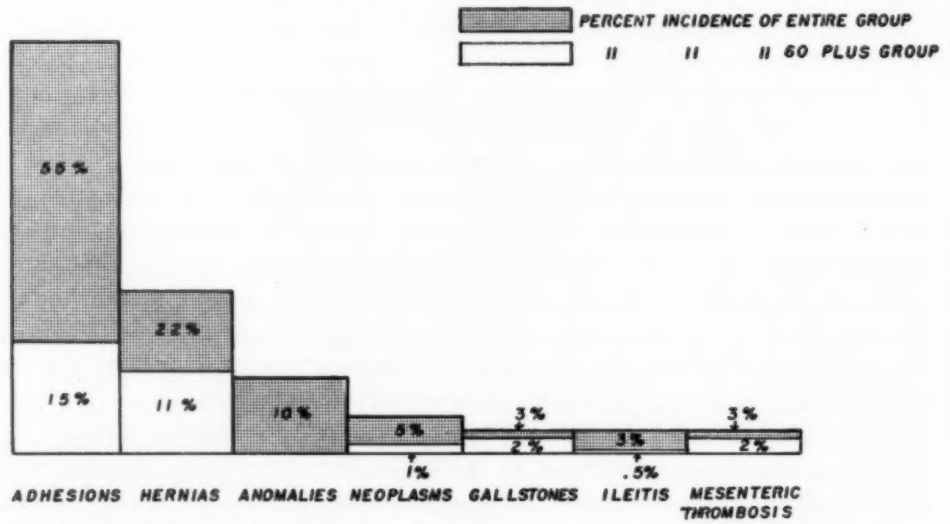


FIG. 1. Incidence of etiologic factors in the overall group compared with the 60-plus age group.

the progressive deterioration of the patient, particularly if elderly, can be extremely rapid. In order to determine this point, the records of those who were treated by definitive conservative therapy were reviewed. Nonoperative treatment was carried out in 68 cases, and although the tube was passed beyond the pylorus in over 80 per cent of the patients, only 32 were relieved permanently. The remaining 36 were those in whom surgical therapy followed varied periods of conservative treatment. It was very interesting to find that when surgery was resorted to within twenty-four hours (10 cases), no deaths ensued. In 26 cases conservative treatment was continued for from twenty-four to one hundred and twenty hours and the mortality was progressive and related to the time period. An additional intriguing fact is that the overall mortality of cases undergoing surgery following a period of unsuccessful decompression was 16.6 per cent, which is twice that (8.3 per cent) in the 130 cases with all types of pathologic conditions requiring immediate surgical therapy. It would seem that the danger of persistent unsuccessful therapy is more than that of immediate surgical intervention.

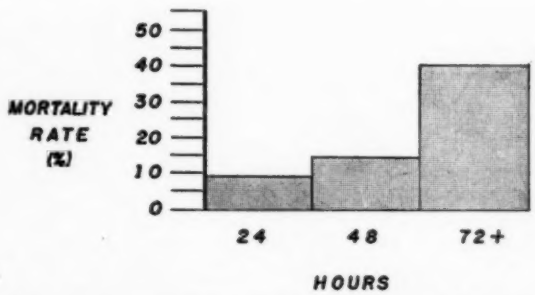


FIG. 2. Relationship between mortality rate and the delay in instituting therapy

Another problem which was related to the mortality was that of closed-loop obstruction, *i.e.*, the intestine is obstructed at two points, thus isolating a loop of bowel, as illustrated by a volvulus or an internal hernia (Fig. 5, a and b). The basis of this difficulty was primarily diagnostic. These patients did not show the classic signs of acute small-bowel obstruction, as indicated by the fact that abdominal distension and typical radiologic findings were noted in less than 50 per cent. The most reliable method of management is that of watchful expectancy and the detection of impending strangulation (increased pain, increased abdominal tenderness, increased pulse rate, development of a palpable mass) and finally, of absolute strangulation (muscle spasm, rebound tenderness, fever, leukocytosis and then shock (6)). Closed-loop obstruction occurred in 10 per cent of our cases and carried a mortality rate of 27 per cent. This mortality was primarily due to delay in diagnosis, as indicated by the 91 per cent incidence of strangulation in these cases.

Obviously, age affects the mortality (Fig. 6). The highest mortality (19.2 per cent) occurred in the 70-plus group and was primarily due to poor renal and cardiac reserve and low resistance to infection. The very young (0–10 years) had the second highest mortality rate (15.3 per cent) as a result of multiple congenital defects and the generally poor surgical risk in the newborn. The

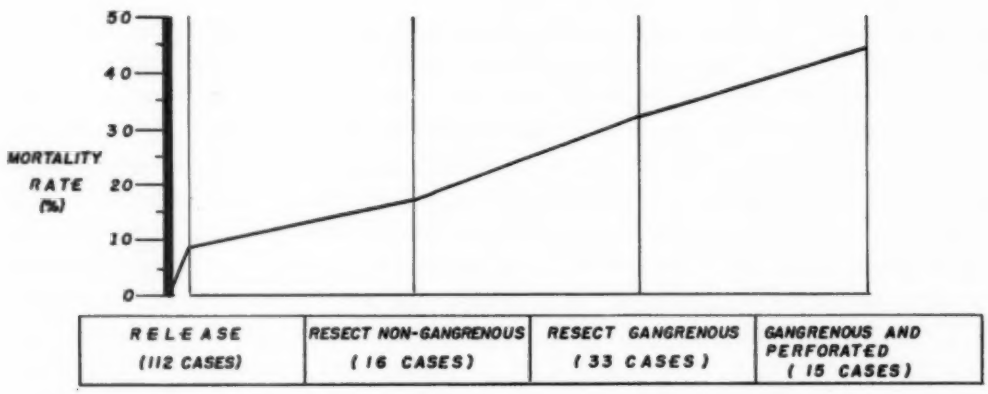
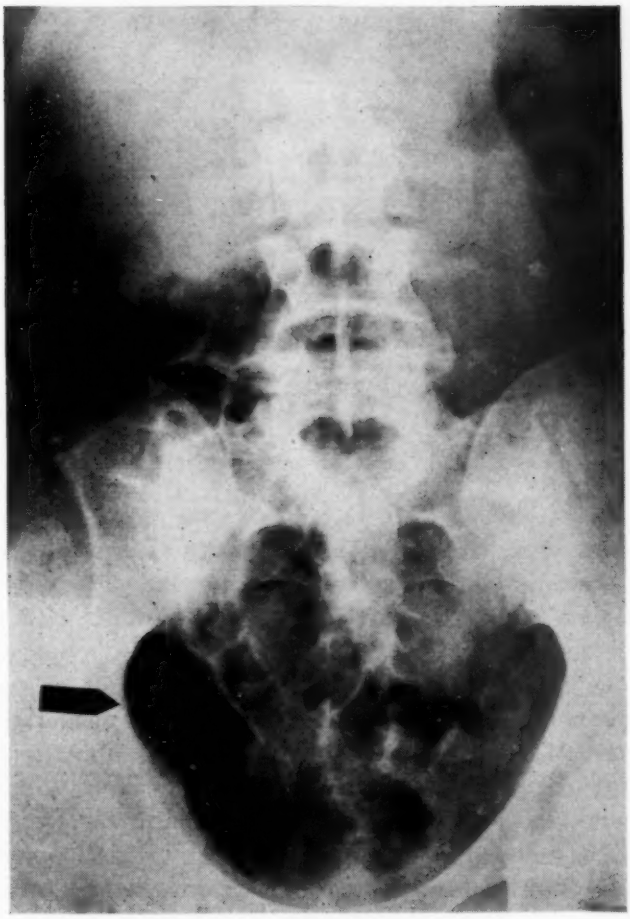
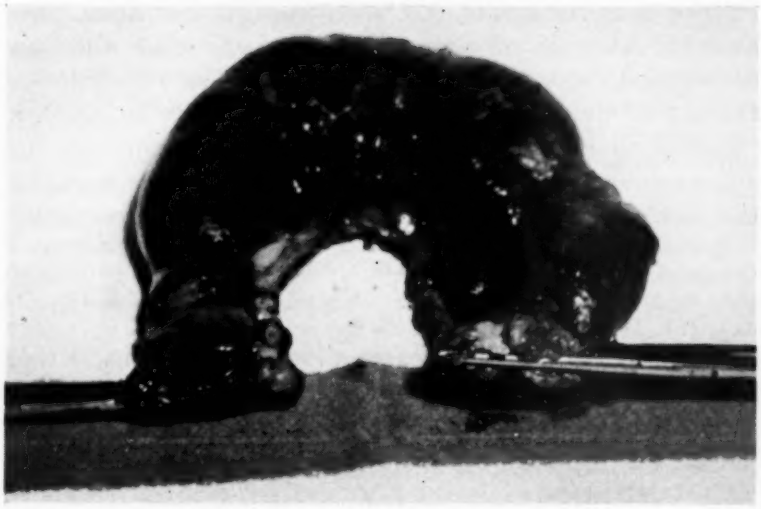


FIG. 3. Relationship between mortality rate and operative procedure in 176 surgical cases (overall mortality rate, 10.2 per cent).

FIG. 4. Roentgenogram showing persistent distended small bowel, typical of a high, simple obstruction of the small bowel.



a



b

FIG. 5. **a**. Roentgenogram showing a strangulated closed-loop small-bowel obstruction (arrow). The dark loop, with loss of its markings, is seen in the right lower quadrant next to a colon packed with feces. **b**. Resected specimen of the small bowel shown in (**a**).

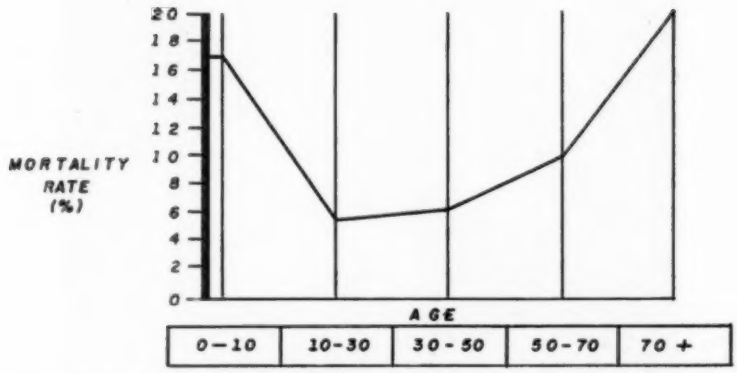


FIG. 6. Relationship between mortality rate and age group

middle-age groups showed a fairly uniform mortality. The influence of age is again noted when the causes of death in the surgical mortalities are reviewed. Cardiac failure accounted for the greatest number of postoperative deaths (28 per cent), and it largely occurred in the older patients with very poor renal and cardiac reserve who did not tolerate hydration. Bronchopneumonia caused 11 per cent of the deaths and also seemed related to age.

Undesired side effects might be largely avoided by limiting one's persistence with nonoperative therapy in the elderly, by early ambulation, and by antibiotic therapy. Shock and peritonitis were the causes of 39 per cent of the deaths. In general, the results could have been improved by earlier diagnosis and therapy. Electrolytic imbalance was the cause of 22 per cent of the fatalities and is probably best avoided by limiting unsuccessful conservative treatment.

SUMMARY

The incidence of acute small-bowel obstruction is increasing, chiefly due to the increased incidence of adhesion bands, in association with the increased number of abdominal laparotomies and the high survival rate of the present-day patient. This study suggests that the mortality rate may be reduced by earlier diagnosis of strangulation, awareness of closed-loop obstruction, limitation of unsuccessful conservative therapy to twenty-four hours, employment of appropriate antibiotics, and judicious use of fluid and electrolyte therapy.

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Abstracts of Current Literature

CHEST SHADOWS IN THE AGING.

Boucot, K. R., *Pennsylvania M. J.* **57:** 1099 (Nov.) 1954.

Shadows in the aging chest are of increasing importance. If chest photofluorograms are made annually in male patients up to age 45 and biannually thereafter, data will become available to date and characterize abnormal pulmonary shadows. In order of importance for survival, the following causes of abnormal shadows must be considered: bronchogenic carcinoma, tuberculosis, suppurative disease, emphysema, the diffuse fibroses, and the rarer diseases. The probability of a given disease is influenced by location, laterality, characteristics, association with or distortion of neighboring structures, and history and symptoms. No rigid rules can be laid down. When sputum is present, it presents a rapid method of identifying tuberculosis. If sputum is not available or does not show tubercle bacilli, negative findings with the tuberculin test rule out tuberculosis except in critically ill patients. Beyond that, the physician's best judgment must be utilized to establish the order of priority for essential diagnostic studies. These include special radiologic examinations like bronchography, planigraphy, barium swallow, bronchoscopy, cytologic studies, biopsy of regional nodes, pulmonary biopsy, and ultimately exploration if necessary. (From author's summary.)

INVESTIGATIONS OF MUSCULAR WEAKNESS IN MIDDLE LIFE: THE SO-CALLED MENOPAUSAL MUSCULAR DYSTROPHY.

Bounin, M., and Adey, W. R., *Australasian Ann. Med.* **3:** 171 (Aug.) 1954.

Six cases of myopathy in middle-aged individuals are reported. Five of these were menopausal muscular dystrophy as described by Shy and McEachern (1951). There were muscular weakness without wasting confined to the proximal muscles, shortening of motor unit action potentials demonstrated by electromyography, and patchy degeneration of muscle histologically. One was a case of acute polymyositis with similar electromyographic changes and patchy necrosis of muscle, but with an acute clinical picture complicated by hypertension and the development of carcinoma of the breast and of a rash resembling that of lupus erythematosus. The significance of the electromyographic findings is discussed. They were consistent with a diagnosis either of muscular dystrophy or of chronic polymyositis. The biopsy findings indicated menopausal muscular dystrophy but the changes may have been the result of nonspecific lesions. Mixed tocopherols in doses of 300 mg. daily produced clinical and electromyographically demonstrated improvement in 2 of 4 patients. Only 1 of 3 patients receiving cortisone improved. This patient had previously received tocopherol so it was not possible to determine whether the further improvement resulted from, or was coincidental with the use of 100 mg. cortisone daily for three weeks and later of testosterone.

FEMINIZING MESENCHYMOMAS OF THE OVARY.

Busby, T., and Anderson, G. W., *Am. J. Obst. & Gynec.* **68:** 1391 (Nov.) 1954.

The Ovarian Tumor Registry sponsored by The American Gynecological Society has collected 1,000 ovarian tumors, 107 of which are feminizing mesenchymomas of the ovary. An incidence of 1 to 4 per cent has been reported, but the exact percentage of feminizing mesenchymomas among ovarian neoplasms is not known. In general, the clinical features of these tumors followed the accepted concepts described in the literature. They can occur at any age. More than half of the patients in the group reported were over 50 years of age. The tumors were of the following types: granulosa-cell, 75; granulosa-theca cell, 19; and

theca-cell, 13. Ninety-six of the 107 patients have been followed five years or more since the primary operation. Among them, 76 (79.2 per cent) are living and 20 (20.8 per cent) are dead within five years. Two additional deaths occurred seven years following surgery (7-year mortality, 22.9 per cent). Two women have had recurrences so that the malignancy of feminizing mesenchymomas is 25 per cent. The gross stage of the disease at operation had the greatest effect on prognosis. The five-year mortality was 11.2 per cent when the neoplasm was confined to one ovary and 42.8 per cent among cases with extension to adjacent structures. Tumors of histologic Grade I were associated with a five-year mortality of 9.5 per cent compared with a 75 per cent mortality in Grade IV. Methods of treatment were variable. Complete evisceration of the pelvic genital tract in patients in the meno pause appears to be important.

CLINICAL PATTERN OF POLYPS OF THE RECTUM AND COLON.

Byrne, R. V., *West. J. Surg.* **62:** 567 (Nov.) 1954.

The failure to realize that most patients beyond 50 years of age who have rectal bleeding probably have a polyp of the colon or rectum and the failure to make adequate and repeated x-ray studies in patients in whom a polyp is suspected are two common errors in the diagnosis and treatment of polyps of the colon and rectum. Patients in the older age group who have rectal bleeding should be examined by the sigmoidoscope, barium enema and air contrast studies of the colon for the presence of polyps. The percentage of diagnosis will depend largely upon the thoroughness of these methods of examination. Since most polyps of the colon and rectum are multiple, the colon must be examined with the sigmoidoscope at the time of surgery. Polyps left in the colon postoperatively are a potential source of carcinoma.

AN UNUSUAL TYPE OF PRESENILE DEMENTIA (ATYPICAL ALZHEIMER'S DISEASE WITH AMYLOID VASCULAR CHANGE).

Corsellis, J. A. N., and Brierley, J. B., *Brain* **77:** 571 (Dec.) 1954.

Two cases of presenile dementia are described. In the first, an hereditary factor may have been present, for in addition to the dementia there were signs of a spastic paresis of one limb. Pathologically the findings in part resembled those of Alzheimer's disease but they also included a severe amyloid vascular change and plaque formation of unusual type and severity. A similar clinico-pathologic syndrome has been described in three other families. The second case also showed the amyloid vascular change in addition to the more usual features of Alzheimer's disease. The histologic findings agreed with the observations of Divry and of Scholz on the amyloid basis of the various changes found at times in the presenile and senile brain. The relationship of the 2 cases to each other, to Alzheimer's disease, and to vascular disease is discussed.

COMPORTAMENTO DELLO IODIO ORGANICO SERICO NELLA VECCHIAIA (THE ORGANIC IODINE IN THE SERUM IN OLD AGE).

Fazio, B.; Costa, U., and Assereto, G., *Arch. Maragliano Patol. Clin.* **9/2:** 511, 1954; Abstr., *Excerpta Med.* (Internal Medicine) **9:** 561 (Apr.) 1955.

Investigations among 102 subjects between the ages of 66 and 90 years revealed that the organic iodine level of the serum decreases with advancing age.

A STATISTICAL COMPARISON OF THE BLOOD LYSOZYME ACTIVITY OF NORMAL ADULTS AND OF PATIENTS WITH LOCALIZED AND GENERALIZED CARCINOMATOSIS.

Fogelson, S. J., and Lobstein, O. E., *Am. J. Digest. Dis.* **21:** 324 (Nov.) 1954.

Lysozyme activity was determined in the blood of 35 cancer patients with localized and/or generalized carcinomatosis and compared with that in 77 normal individuals previ-

ously reported. The former had a statistically higher blood lysozyme activity that was neither diagnostic nor clinically significant. Comparison of the distribution curves showed the curve for the carcinoma group to be distorted into the upper limits of lysozyme activity of the blood, but no normal individual had over 12 micrograms of lysozyme per cubic centimeter of blood. Furthermore, none of the carcinoma patients had less than 4 micrograms of lysozyme per cubic centimeter of blood. This observation warrants further study.

ACTION OF TRIETHANOLAMINE TRINITRATE IN ANGINA PECTORIS.

Friend, D. G.; O'Hare, J. P., and Levine, H. D., *Am. Heart J.* **48:** 775 (Nov.) 1954.

Triethanolamine trinitrate in doses of 2 mg. orally four times daily, was ineffective in the treatment of angina pectoris. Nitroglycerin in similar dosage was no better than a placebo. Both were well tolerated and no toxic reactions were observed during administration for two to four weeks.

NEWER CLINICAL AND LABORATORY STUDIES IN THE AGED. III. URINARY TEST FOR GASTRIC SECRETION OF HYDROCHLORIC ACID IN PATIENTS 80 TO 100 YEARS OF AGE.

Goldbloom, A. A.; Hadra, E. G.; Pomeranze, J., and Rechtschaffen, J., *Am. J. Digest. Dis.* **21:** 321 (Nov.) 1954.

Diagnex, a quininium resin indicator, which operates through a displacement of quinine by the hydrogen ions of the gastric hydrochloric acid, may be used to determine gastric acidity. The quinine hydrochloride formed is absorbed by the small intestine, appears in the urine within two housr after ingestion, and produces fluorescence. The results of the test are not quantitative. By this so-called tubeless gastric acidity test, achlorhydria was found in 30 per cent of 95 "normal" geriatric patients 80 to 100 years of age, and acidity in 70 per cent. Roentgenograms showed a normal gastro-intestinal tract in 52 per cent of the patients. One gastric carcinoma, 2 gastric ulcers, and 1 duodenal ulcer were found. Positive tubeless gastric acidity values (69.5 per cent) approximated the normal and varied insignificantly from gastrointestinal x-ray findings (70.4 per cent). The 29 patients with achlorhydria by the tubeless method were checked by gastric intubation. Three positive results were obtained, showing a discrepancy of 11.1 per cent between the methods. The urinary test for gastric secretion of hydrochloric acid is advocated for geriatric patients and in conditions that contraindicate intubation. Its convenience and economy make it possible to screen large numbers of patients and eliminate unnecessary x-ray examinations.

MITRAL VALVE DISEASE OVER THE AGE OF 50.

Hebbert, F. J., and Rankin, J., *Acta med. Scandinav.* **150:** 101, 1954, Fasc. 2.

Rheumatic heart disease is more common in the elderly than was realized until recently. The physical signs that once were ascribed to arteriosclerotic disease are frequently rheumatic in origin. Failure to diagnose this type of case in the older age group may be due to a tendency to dismiss rheumatic valvular disease from the differential diagnosis. One hundred and six cases of rheumatic mitral disease are reviewed. The diagnosis was made or confirmed at necropsy in 57. No postmortem examination was performed in 13. Thirty-six patients are still living. Clinical diagnosis accomplished in 75 patients was based on the presence at some time during the observation period of a rough low-pitched murmur in middle or late diastole, audible at or medial to the apex. When interpretation was doubtful, diagnosis was confirmed by radiologic demonstration of enlargement of the left ventricle. Other signs indicative of mitral stenosis were usually present. The causes of death among the patients examined post mortem were: unconnected disease in 12, congestive heart failure in 22, major systemic emboli in 16, and pulmonary infarction in 3. In 4 others,

it was doubtful whether mitral stenosis contributed to the cause of death. The numerous complicating conditions included 8 cases of bacterial endocarditis. Among the patients with a history of previous illness, 48.7 per cent had a history of acute rheumatism or chorea. The average age of infection was 22.5 years. Many women with a history of several pregnancies survived to old age despite mitral valvular disease. Dyspnea on exertion was the principal symptom. As a cause of disability, it was often related to the onset of auricular fibrillation. Hypertension exceeded 150/90 in 39 per cent of the patients and 190/110 in 26 per cent. Longevity in elderly patients with rheumatic valvular disease is ascribed to a number of causes, most important among which seem to be late onset and the absence of recurrent rheumatic infection. The onset of mitral stenosis in the later decades of life is a gradual process and in many cases may be regarded as benign.

SCURVY IN OLD AGE.

Hughes, W., and MacLennan, D. C., *Brit. M. J.* **2:** 1149 (Nov. 13) 1954.

Mild degrees of nutritional deficiency frequently occur in elderly people who live alone but gross deficiencies like scurvy and pellagra are rare. A case of scurvy is reported in an elderly man with mental deterioration living alone after the death of his wife (a senile dement) and whose house showed no evidence of recent cooking. The scurvy and his general condition improved after treatment with vitamin C and later with iron and vitamin B complex but his mental condition remained unaltered. In this case, funds were available to provide an adequate diet had either partner been mentally competent to spend them for this purpose. Other cases cited of scurvy in elderly individuals resulted from diets limited to tea and bread with occasional meat and the absence of meals with potatoes and vegetables.

SERUM PROTEINS AND LIPOPROTEINS IN MULTIPLE MYELOMATOSIS.

Lewis, L. A., and Page, I. H., *Am. J. Med.* **17:** 670 (Nov.) 1954.

The bizarre protein patterns in multiple myelomatosis suggested that lipoproteins might also show anomalies. Studies were made of the serum of 24 patients with multiple myeloma, 4 of whom also had arteriosclerotic heart disease and 6 marked renal insufficiency. The serum lipoprotein pattern studied by ultracentrifugation showed normal concentrations of -S > 70, 40–70 (γ_1-globulin) and -S20–25 (α_2-lipoprotein). Values below normal were found for -S25–40 (β_1-lipoprotein) and -S1–10 (α_1-lipoprotein). Serum cholesterol concentrations were below those for normal people of like age and sex. The electrophoretic protein patterns showed increased concentrations of components with mobility of β_1-, γ_1-, or γ_2-globulin. The changes in lipoprotein did not correlate with electrophoretic protein patterns. However, sera with the largest globulin concentrations usually had very low concentrations of β_1- and α_1-lipoproteins and cholesterol.

I TUMORI DELL'ETÀ SENILE (TUMORS IN AGED SUBJECTS).

Lovenati, M., and Fogher, L., *Rass. giul. med.* **10/2:** 39, 1954; Abstr., *Excerpta Med.* (Cancer) **2:** 884 (Nov.) 1954.

The study of a large number of cases of tumor in subjects over 70 years of age revealed some interesting features with regard to the incidence of tumors in old age (high in the pancreas and skin, low in the ovary, uterus, and oral cavity) and their course, which is usually slower than that in other age groups.

THE CLINICAL FEATURES OF AORTIC STENOSIS.

Mitchell, A. M.; Sackett, C. H.; Hunzicker, W. J., and Levine, S. A., *Am. Heart J.* **48:** 684 (Nov.) 1954.

Because of present interest in the surgical treatment of aortic stenosis, its clinical features are delineated by a review of 533 patients in four groups: pure aortic stenosis

(AS); aortic stenosis with insufficiency (ASI); aortic and mitral stenosis (AMS), and trivalvular stenosis (TS). The majority of cases, even of the calcific type were rheumatic in origin. Rheumatic fever was more frequent in the history of patients with AMS than with AS. Males predominated among AS cases, females in TS, and the sexes were evenly distributed in AMS. The average age at death (*in years*) was: among 326 known fatal cases, 52.2; AS, 65.3; ASI, 52.5, AMS, 48.4; and TS, 36.5. The average duration of life (*in months*) after onset of congestive failure was 42.5; for AS, 22.7; ASI, 28.9; AMS, 56.4; and TS, 80.0. With a history of rheumatic fever, the interval between the attack and the onset of failure (*in years*) varied as follows: AS, 47.6; ASI, 34.2; AMS, 28.2; and TS, 14.6. The *percentile* incidence of angina pectoris was 29.8; AS, 36.7; ASI, 34.8; AMS, 20.8; and TS, 10.4. Aortic insufficiency did not increase its incidence. The duration of life was about four years after onset of the disease, regardless of the valves involved. Coronary vessels were significantly sclerosed in most cases of angina but a small number of elderly individuals and some younger ones had normal coronary vessels. In them the degree of aortic stenosis was not necessarily great but the heart weight was likely to be markedly increased. Syncope occurred in the following percentages of patients: entire series, 12.6; AS, 20.6; AMS, 10.0; and TS, 3.5. The average duration of life after onset was three years in all groups. A high degree of stenosis of the aortic valve was usually present in these cases. Sudden death occurred in 23.4 per cent of patients in whom the mode of death was known (excluding subacute bacterial endocarditis) and at an average age of 52 years. Mitral stenosis did not affect the incidence, nor did syncope predispose toward it, but there was frequently a past history of angina. Most of the patients had significant coronary sclerosis but the degree of stenosis of the aortic valve was the same as in those who did not die suddenly. The mode of death among 214 cases (*in per cent*) was: instantaneous, 18.7; congestive failure, 35; pneumonia, 8.8; subacute bacterial endocarditis, 20.1; myocardial infarction, 2.3; pulmonary emboli, 4.6; cerebrovascular accidents, 4.2; and miscellaneous causes, 6.4. Conduction disturbance was present in 26 per cent of 455 cases in whom electrocardiographic tracings were available. Left bundle-branch block was more frequent in AS than in AMS. Auricular fibrillation was present in 10 per cent of AS cases and in 55 per cent of AMS cases. The prognosis was grave in the former when the blood pressure was normal and better when hypertension was also present. Left ventricular hypertrophy was found in 74.8 per cent of 127 patients, in 84 per cent of those with AS, and in 51 per cent of those with AMS. In AS, this indicated a slight degree of aortic stenosis, but in AMS its presence or absence did not reflect the degree of aortic stenosis. Blood pressure levels were not helpful in diagnosis. Lower systolic levels were more commonly observed with a higher degree of stenosis and lower diastolic levels in ASI. The most constant finding was a systolic murmur, generally loudest at or near the second right intercostal space, of an average intensity of 3.6, unaffected in intensity by the blood pressure level, and decreased by the presence of congestive failure. A systolic thrill was palpable only when a murmur of grade 3 or 4 or louder was present. The aortic second sound was decreased or absent in most AS cases, but in many instances the sound was normal or increased, especially if hypertension were present. A forceful or lifting apex impulse proved to be a valuable indication of left ventricular hypertrophy. A plateau pulse was a helpful sign. Subacute bacterial endocarditis was found in 10 per cent of the cases. A calcified aortic valve was the most valuable roentgenologic finding. Only a slightly greater degree of stenosis accompanied the finding. A calcified valve may be detected in the third or fourth decade. The BMR was moderately elevated (average +33.5 per cent) in 29 of 72 patients tested. Average heart weights (*in grams*) were: AS, 606; ASI, 686; AMS, 593; and TS, 543. It is concluded that aortic stenosis can be diagnosed accurately but the degree of stenosis predicted with only a moderate degree of accuracy.

THE FATE OF CLINICALLY UNRECOGNIZED INTRACRANIAL MENINGIOMAS.
Moore, M. T., *Neurology* **4:** 837 (Nov.) 1954.

Ten cases of intracranial meningioma are presented and the factors that led to clinical failure or error in diagnosis considered in an effort to determine the reasons why meningi-

omas may not be recognized and why there may be doubt concerning the cell type of tumor and consequent treatment. Brain tumor was suspected in only 2 of the patients upon admission. Headache and mental disturbances headed the list of symptoms. As these appear commonly in elderly individuals as the result of vascular hypertension, cardiovascular disorders, and cerebral manifestations incident to senility, these diagnostic possibilities tend to be considered to the exclusion of brain tumor. Likewise, the most frequently occurring signs—disordered motor function, mental abnormalities, and altered states of consciousness—are also the most common occurrences in cerebrovascular disease, hypertension, metabolic disorders, and cardiorenal disease as found in the aged. Awareness of this similarity points up the need to rule out brain tumor. In 5 of the series of 10 patients there was a sudden apoplectiform onset, commonly associated with gliomata. The initial diagnosis was cerebral thrombosis or hemorrhage. Four of the patients died within twenty-four hours and 1 six days postoperatively. Meningioma was found at autopsy. Among the 5 cases in which enough key signs were recognized and in which study revealed the presence of an intracranial space-occupying lesion, 3 were considered from clinical evidence to be gliomas. Craniotomy was performed in 2 of the latter because malignant glioblastoma was suspected in each and could not be differentiated from benign meningioma by clinical criteria alone. This course was justified because all 10 of the meningiomas in this series proved to be in readily accessible areas of the intracranial cavity. Only 1 of the 5 patients survived more than twenty-four days postoperatively. The need for "tumor-consciousness," adequate study, and/or operative exposure of an intracranial tumor which evidence indicates to be a rapidly invasive glioblastoma, are emphasized.

PSYCHIATRIC ILLNESS IN THE ELDERLY. A FOLLOW-UP STUDY.

O'Connell, B. A., *Brit. M. J.* **2:** 1206 (Nov. 20) 1954.

One hundred and nineteen patients aged 65 and over, being the unselected admissions to a mental hospital during one year, were followed at intervals of six months, twelve months, and two years. Only slightly more than half of the cases belonged to the senile dementia and arteriosclerotic groups and had a relatively poor outcome. Between one-quarter and one-third were cases of affective disorder, and were found to be clinically distinguishable from cases associated with senile or arteriosclerotic cerebral disease. Affective disorder was found to be a benign illness, in contrast to senile dementia and arteriosclerotic disease. The results of electrical treatment in 26 of the 33 cases of affective disorder proved satisfactory. It is concluded that in patients of this age group every effort must be made to differentiate the affective cases from those of senile dementia and cerebral arteriosclerosis. If the physical condition of the patient permits, electrical treatment should be considered. Age as such is no barrier to the use of this treatment, and even when the physical condition is not perfect the risks of treatment must be balanced against the misery of a protracted illness. (From author's summary.)

CHRONIC BRONCHITIS—A NEGLECTED DISEASE ENTITY.

Phillips, R. W.; Phillips, A. M., and Pecora, D. V., *Dis. of Chest* **24:** 520 (Nov.) 1954.

Simple chronic bronchial irritation appears to be the most common cause of chronic cough. Chronic bronchitis is significant as a disease entity, as it frequently causes pulmonary emphysema. The mechanisms whereby this takes place are discussed. Among 18 males aged 50 to 69 years with cough of ten or more years' duration, the inhalation of cigarette smoke was found to be the common agent in the production of chronic bronchitis. No other cause for cough was demonstrated. All raised sputum and showed evidence of pulmonary emphysema, usually of severe degree in long-standing cases. A study of 20 cases with autopsy evidence of pulmonary emphysema and without tuberculosis, tumor, or asthma, showed chronic bronchitis in all and only associated bronchial disease in 18. Bronchiectasis was found in 2 cases.

THE CAPSULE OF THE PROSTATE.

Power, S., *Lancet* **2:** 1099 (Nov. 27) 1954.

Some undesirable sequelae of prostatectomy may be avoided by leaving a clean-walled cavity instead of a ragged one. This end is most likely to be achieved by starting the enucleation from below upwards at the apices, continuing from above downwards behind the middle lobe, and finishing in front along the anterior commissure. (Author's summary.)

ÜBER POLSTERARTIGE VERDICKUNGEN PROXIMAL DER HANDGELENKE (CUSHION-LIKE THICKENING PROXIMAL TO THE WRIST JOINT).

Schimpf, A., *Endokrinologie* **32:** 57, 1954, Heft 1–2.

Three cases of local fat pads proximal to the wrist joint in elderly women are reported. Such fat deposits occur in women of pyknic physique with slender shaped wrist joints. The cushions form gradually in the fifth decade of life, usually at the beginning of, or during the menopause and appear to be related to hormonal alterations during the climacteric. This is a frequently observed anomaly which, as the literature shows, seems previously to have gone unnoticed. Differentiation between these fat deposits and swellings in the area of the wrist joint is discussed.

ORAL METRAZOL THERAPY IN CEREBRAL ARTERIOSCLEROSIS.

Sommer, R. J., *Illinois M. J.* **106:** 323 (Nov.) 1954.

In 19 male patients with cerebral arteriosclerosis, with or without psychosis, Metrazol was administered orally in a dose of 18 grains daily for thirty days, 12 grains daily for thirty days, and then 6 grains daily for thirty days. No untoward effects occurred except excitement and restlessness in 1 patient at the higher dosage. This patient and 5 others remained unchanged, 2 showed slight improvement, 9 moderate improvement, and 2 marked improvement. Appetite and sleep were affected first, followed by changes in adjustment, orientation and behavior. The maintenance dosage could not be lowered without regression in a few weeks. These results indicate that oral Metrazol therapy has a place in the treatment of cerebral arteriosclerosis in the aged and is worthy of trial, especially in view of the generally unsatisfactory results of other forms of treatment in this class of patients.

BOOKS RECEIVED

Ciba Foundation Colloquia on Ageing. Volume I. General Aspects. Edited by G. E. W. Wolstenholme, Director and Secretary to the Executive Council, and Margaret P. Cameron, Scientific Assistant, The Ciba Foundation. Cloth. $6.75. Pp. 255. J. & A. Churchill Ltd., London; and Little, Brown and Company, Boston, 1955.

Breast Cancer and Its Diagnosis and Treatment. By Edward F. Lewison, M.D., Assistant Professor of Surgery, Johns Hopkins University School of Medicine, Baltimore. Cloth. $15. Pp. 478. Williams & Wilkins Company, Baltimore, 1955.

Clues in the Diagnosis and Treatment of Heart Disease. American Lecture Series, No. 242. By Paul D. White, M.D., Consultant in Medicine, Massachusetts General Hospital, and Past Clinical Professor of Medicine, Harvard University, Boston. Cloth. $5.50. Pp. 186. Charles C Thomas, Publisher, Springfield, Illinois, 1955.

The Biologic Effects of Tobacco. Edited by Ernest L. Wynder, M.D., Head, Section of Epidemiology, and Associate, Sloan-Kettering Institute for Cancer Research, New York. Cloth. $4.50. Pp. 215. Little, Brown and Company, Boston, 1955.

The Health of the Elderly at Home. By William Hobson, M.D., Professor of Social and Industrial Medicine, University of Sheffield, and John Pemberton, M.D., Senior Lecturer in Social and Industrial Medicine, University of Sheffield, England. Cloth. Pp. 238. Butterworth & Company, Ltd., London, 1955.

The Psychological Variables in Human Cancer. A Symposium presented at the Veterans Administration Hospital, Long Beach, California. Edited by Joseph A. Gengerelli, Professor of Psychology, University of California at Los Angeles, and Frank J. Kirkner, Chief Clinical Psychologist, Veterans Administration Hospital, Long Beach, California, and Associate Clinical Professor of Psychology, University of California at Los Angeles. Cloth. $3.00. Pp. 135. University of California Press, 1954.

Emotional Problems and What You Can Do about Them. By William B. Terhune, M.D., Medical Director, Silver Hill Foundation, New Canaan, Connecticut, and Associate Clinical Professor of Psychiatry, Yale University School of Medicine, New Haven, Connecticut. Cloth. $3.00. Pp. 190. William Morrow & Company, New York, 1955.

Experiencing the Patient's Day. By Robert W. Hyde, M.D., Assistant Superintendent, Boston Psychopathic Hospital, Boston. Paper. $2.20. Pp. 214. G. P. Putnam's Sons, New York, 1955.

1955 *Medical Progress.* Edited by Morris Fishbein, M.D. Cloth. $5.00. Pp. 246. McGraw-Hill Book Company, Inc., New York, 1955.

Casimir Funk. Pioneer in Vitamins and Hormones. By Benjamin Harrow, Professor Emeritus, Department of Chemistry, City College of New York. Cloth. $4.00. Pp. 209. Dodd, Mead and Company, New York, 1955.

Textbook of Chiropody. Second edition. By Margaret J. McKenzie Swanson, Co-Founder of Edinburgh Foot Clinic and School of Chiropody, Edinburgh, Scotland. Cloth. $5.00. Pp. 268. Williams & Wilkins Company, Baltimore, 1954.

Financing Hospital Care in the United States. Volume I. Factors Affecting the Costs of Hospital Care. Edited by John H. Hayes. Cloth. $4.00. Pp. 300. The Blakiston Company, Inc., New York, 1954.

Financing Hospital Care in the United States. Volume II. Prepayment and the Community. Edited by Harry Becker. Cloth. $4.50. Pp. 356. The Blakiston Division, McGraw-Hill Book Co., Inc., New York, 1955.

Financing Hospital Care in the United States. Volume III. Financing Hospital Care for Nonwage and Low-Income Groups. Edited by Harry Becker. Cloth. $2.50. Pp. 110. The Blakiston Division, McGraw-Hill Book Co., Inc., New York, 1955.

The Medical Care of the Aged and Chronically Ill. By FREDDY HOMBURGER, M.D., Research Professor of Medicine, Tufts College Medical School, Boston. Cloth. $5.75. Pp. 253. Little, Brown and Company, Boston, 1955.

University of California Publications in Public Health. Volume II. Investigations on Genetic Aspects of Carcinoma of the Stomach and Breast. By CHARLES M. WOOLF. Paper. $1.00. University of California Press, Berkeley and Los Angeles, 1955.

In keeping with the objectives of the Society to make readily available to the medical profession knowledge of the latest clinical practices having to do with this broad field

THE AMERICAN GERIATRICS SOCIETY

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The Roosevelt Hotel in New York has set aside a number of rooms to take care of physicians attending this symposium. Those who plan to attend should write to Mr. A. G. Schellenberg, Reservation Manager, Hotel Roosevelt, Madison Avenue at 45th Street, New York 17, New York. Mention that you will attend the symposium and Mr. Schellenberg will be glad to take care of your needs.

The American Geriatrics Society

PROGRAM

GRADUATE SYMPOSIUM ON GERIATRIC MEDICINE

Presented by
THE AMERICAN GERIATRICS SOCIETY

Wednesday, November 30 and Thursday, December 1, 1955
PALM TERRACE SUITE

HOTEL ROOSEVELT

MADISON AVENUE AND 45TH STREET

NEW YORK CITY

Morning Session, Wednesday, November 30

Edward Henderson, M.D., presiding

9:00–10:00

CHEMOPALLIDECTOMY: A NEUROSURGICAL TECHNIQUE USEFUL IN GERIATRIC PARKINSONIANS

Irving S. Cooper, M.D. and Nicolas Poloukhine, M.D.*†—*Assistant Professor of Neurosurgery, New York University-Bellevue Medical Center.† Director, Department of Neurosurgery, St. Barnabas Hospital, New York City.

10:00–10:15

Recess for refreshments

10:15–10:45

OSTEOPOROSIS: DIAGNOSIS AND TREATMENT

Marvin Weinberg, M.D., New York City.

10:45–11:15

SURGERY AND ANESTHESIA AS A TEAM FOR GERIATRIC SURGERY

Frank Glenn, M.D. and Joseph Artusio, M.D.*†—*Professor of Surgery, Cornell University Medical College, and Surgeon-in-Chief, New York Hospital. †Associate Professor of Surgery (Anesthesiology), Cornell University Medical College, and Attending Anesthesiologist in Charge, New York Hospital, New York City.

11:15–11:45

THYROID FUNCTION AND DISEASE IN OLD AGE

Thomas H. McGavack, M.D., Professor of Clinical Medicine, New York Medical College, Flower and Fifth Avenue Hospitals, New York City.

11:45–12:15

TREATMENT OF PULMONARY DISEASES IN OLDER PEOPLE

Alvan L. Barach, M.D., Clinical Professor of Medicine, Columbia University, College of Physicians and Surgeons, and Associate Attending Physician, Presbyterian Hospital, New York City.

Afternoon Session, Wednesday, November 30

Laurance W. Kinsell, M.D., presiding

2:00–2:30

A NEW INTRAVENOUS ANESTHETIC WITH REFERENCE TO ITS USE IN ELDERLY PATIENTS

Emery A. Rovenstine, M.D., Professor and Chairman, Department of Anesthesiology, New York University Post-Graduate Medical School, New York City.

2:30–3:00

BREAST CANCER IN THE POST-MENOPAUSAL FEMALE

Frank E. Adair, M.D., Associate Professor of Clinical Surgery, Cornell Medical School, New York City.

3:00–3:30

OBESITY AND DIABETES

C. N. H. Long, M.D., Sterling Professor of Physiology and Chairman, Department of Physiology, Yale University, School of Medicine, New Haven, Connecticut.

3:30–3:45

Recess for refreshments

3:45

PANEL ON HEART DISEASE

Moderator: *Charles T. Stone, Sr., M.D.*, Professor of Internal Medicine, University of Texas, Medical Branch, Galveston, Texas.

David Lehr, M.D., Professor and Director of Pharmacology and Associate Professor of Medicine, New York Medical College, Flower and Fifth Avenue Hospitals, New York City.

Wesley E. Peltzer, M.D., Assistant Clinical Professor of Medicine, University of Utah School of Medicine, Salt Lake City, Utah.

Harold E. B. Pardee, M.D., Associate Professor of Clinical Medicine, Cornell University Medical School, New York City.

Harry Gold, M.D., Professor of Clinical Pharmacology, Cornell University Medical School, New York City.

Robert L. Levy, M.D., Professor of Medicine, Emeritus, Columbia University, College of Physicians and Surgeons, New York City.

Morning Session, Thursday, December 1

Thomas H. McGavack, M.D., presiding

9:00–9:30

DERMATOSES IN THE AGED

Charles Rein, M.D., Associate Professor of Dermatology and Syphilology, New York University Post-Graduate Medical School, New York City.

9:30–10:00

THE MANAGEMENT OF ALLERGIC DISORDERS IN THE GERIATRIC PATIENT

John M. Sheldon, M.D., Professor of Internal Medicine; Director, Department of Post-Graduate Medicine, University of Michigan Medical School, Ann Arbor, Michigan.

10:00–10:15

Recess for refreshments

10:15–10:45

NUTRITION AND THE GERIATRIC PATIENT

Fredrick J. Stare, M.D., Professor of Nutrition, and Chairman, Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts.

10:45–11:15

ACUTE AND CHRONIC CORTICOID THERAPY IN OLDER PEOPLE

Laurance W. Kinsell, M.D., Director, Institute for Metabolic Research, Highland Alameda County Hospital, Oakland, California.

11:15–11:45

INDICATIONS FOR STEROID HORMONE THERAPY IN THE GERIATRIC PATIENT

Robert B. Greenblatt, M.D., Professor of Endocrinology, Medical College of Georgia, Augusta, Georgia.

11:45–12:15

PREDNISOLONE IN THE MANAGEMENT OF LEUKEMIA IN THE ADULT

Joseph M. Hill, M.D., Director, Wadley Research Institute and Blood Center, Dallas, Texas.

Afternoon Session, Thursday, December 1

Edward B. Allen, M.D., presiding

2:00–3:15

PANEL ON RHEUMATIC DISEASES

Moderator: *Walter Bauer, M.D.*, Jackson Professor of Clinical Medicine, Harvard Medical School, and Chief, Medical Services, Massachusetts General Hospital, Boston, Massachusetts.

Russell L. Cecil, M.D., Medical Director, Arthritis and Rheumatism Foundation; Professor of Clinical Medicine, Emeritus, Cornell University Medical School; Consultant Physician, New York Hospital, New York City.

Richard H. Freyberg, M.D., Associate Professor of Clinical Medicine, Cornell University Medical School, and Director, Section on Rheumatic Diseases, Hospital for Special Surgery, New York City.

Joseph Lee Hollander, M.D., Associate Professor of Clinical Medicine, and Chief, Arthritis Section, University of Pennsylvania School of Medicine, and Associate Professor of Medicine, and Chief, Division of Rheumatology, Graduate School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.

Charles Ragan, M.D., Associate Professor of Medicine, Columbia University, College of Physicians and Surgeons, New York City.

3:15–3:30

Recess for refreshments

3:30–4:00

SOCIAL AND ECONOMIC ASPECTS OF OLD AGE

Clark Tibbitts, Editor, *Aging*, and Chairman, Committee on Aging, Department of Health, Education and Welfare, Washington, D. C.

4:00–4:30

EMOTIONAL NEEDS OF OLDER PEOPLE

David C. Wilson, M.D., Professor of Neurology and Psychiatry, and Chairman, Department of Neurology and Psychiatry, University of Virginia School of Medicine, Charlottesville, Virginia.

4:30–5:30

PANEL ON SOME PSYCHOLOGIC AND PSYCHIATRIC PROBLEMS OF OLD AGE

Moderator: *Edward B. Allen, M.D.*, Westchester Division, New York Hospital, White Plains, New York.

Hollis E. Clow, M.D., Westchester Division, New York Hospital, White Plains, New York.

Clark Tibbitts, Editor, *Aging*, and Chairman, Committee on Aging, Department of Health, Education and Welfare, Washington, D. C.

David C. Wilson, M.D., Professor of Neurology and Psychiatry, and Chairman, Department of Neurology and Psychiatry, University of Virginia, School of Medicine, Charlottesville, Virginia.